The neurobiology of stress management

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REVIEW

Abstract

BACKGROUND AND OBJECTIVE: Stress is natural and belongs to life itself. To sustain it and even grow with it biology invented different mechanisms, since stress resistance is obligatory. These pathways, we surmise, can be activated and learned intentionally, through professional stress management training or 'mind-body medicine', or endogenously and automatically through autoregulation. Since the primary goal of various stress-reducing approaches is corresponding, we expect to find an overlapping physiology and neurobiological principle of stress reduction. These common pathways, as we speculate, involve some of the very same signalling molecules and structures. **METHODS**: Concepts of stress and stress management are described and then associated with underlying molecular and neurobiological pathways. Evidence is gathered from different sources to substantiate the hypothesis of an overlapping neurobiological principle in stress autoregulation. **RESULTS**: Stress describes the capacity and mechanisms to sustain and adjust to externally or internally challenging situations. Therefore, organisms can rely on the endogenous ability to self-regulate stress and stressors, i.e., autoregulatory stress management. Stress management usually consists of one to all of the following instruments and activities: behavioral or cognitive, exercise, relaxation and nutritional or food interventions (BERN), including social support and spirituality. These columns can be analyzed for their underlying neurobiological and autoregulatory pathways, thereby revealing a close connection to the brain's pleasure, reward and motivation circuits that are particularly bound to limbic structures and to endogenous dopamine, morphine, and nitric oxide (NO) signalling. Within this work, we demonstrate the existence of opioid, opiate, dopamine and related pathways for each of the selected stress management columns. **DISCUSSION**: Stress management techniques may possess specific and distinct physiological effects. However, beneficial behaviors and strategies to overcome stress are, as a more general principle, neurobiologically rewarded by pleasure induction, yet positively and physiologically amplified and reinforced, and this seems to work via dopamine, endorphin and morphine release, apart from other messenger molecules. These latter effects are unspecific, however, down-regulatory and clearly stress-reducing by their nature. **CONCLUSIONS**: There seems to exist a common neurobiological mechanism, i.e., limbic autoregulation, that involves dopamine, morphine and other endogenous signalling molecules, e.g., other opioid receptor agonists, endocannabinoids, oxytocin or serotonin, many of which act via NO

release, and this share seems to be of critical importance for the self-regulation and management of stress: stress management is an endogenous potential.

Introduction

Stress has gained remarkable significance in our times. Various reasons may account for this. There is the notion of an acceleration of human activities, challenges, productivities, and behaviours, accompanied by increasing levels of noise, pollution and "daily stressors", e.g., having a job or not having a job, some of these stressors related to over-population or actual financial crisis [Adler, 2009; Esch, 2002f; Howards, 2000; Stuckler & Basu 2009]. Whether stress is really and overall increasing or not, the perception of stress certainly is [Esch, 2002f; Esch, 2003d; Metz et al. 2009]. Therefore, we see a surge of stress-related complaints and diseases, many of them leading to medical interventions and, quite often, to cost-expensive treatments and disabilities [Adler, 2009; Croft et al. 2009; Gottholmseder et al. 2009; Rousit et al. 2007].

Hence, the increase in stress awareness may have created a stress epidemic. Science and medicine have deliberately examined, or were they forced to face, the stress phenomenon and its implications for health and treatment options [Esch, 2002f; Stefano, 2005a]. This science has led to expanded knowledge on stress and its management (stress management (SM)), i.e., pharmaceutical and especially non-pharmaceutical means as a remedy [Blumenthal et al. 2005; Ernst et al. 2008; Ernst et al. 2009; Esch, 2003d; Esch et al. 2003b; Esch & Stefano, 2007b; Esch et al. 2007a; Esch, 2008a; Komaroff, 2001; Michalsen et al. 2005; Schwartz, 1980, Stauder et al. 2009]. New medical strategies, named, for example, 'integrative' or 'mind-body medicine' as well as complementary/alternate medical approaches, were invented particularly to focus upon our innate self-healing capacities, i.e., self management, and the autoregulatory capacities that we all possess to effectively respond to the stressors of daily life.

Recent research on stress and SM has revealed a close connection between the clinical features, appearance, and consequences of stress as well as with brain mechanisms of reward, pleasure and motivation, i.e., neurobiology [Esch & Stefano, 2004c]. In particular, limbic autoregulatory paths in the brain that get activated in stress and physiological stress response processes have gained scientific interest [Stefano & Esch, 2005c], and it now seems time to put theses various findings in a broader frame and perspective, especially by linking endogenous SM capacities (usually involving elements of positive behaviors, nutrition, exercise, and relaxation techniques [Esch, 2008a; Esch & Stefano, 2007b; Esch et al. 2006b]) to autoregulatory dopamine, opioid, opiate and nitric oxide signalling pathways [Stefano & Kream 2009c].

There appears to exist a physiological and neurobiological commonalty, at least to a large extent, between the various self-healing-associated activities to fight stress, and the endogenous molecular pathways involved in these very same activities. Our hypothesis is that, due to biological significance of the stress phenomenon for evolution and survival of the individual and its species, successful activities to fight stress were physiologically and genetically conserved and passed on to following generations, thus accounting for a neurobiological overlap in SM strategies. This hypothesis will be examined further in the following sections.

What is stress?

Stress is a natural, biological and, at times, useful phenomenon. Stress describes the effects of psychosocial and environmental factors on physical or mental well-being [Esch, 2003d, Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d; Stefano et al. 2005a; Seyle, 1975]. Stressors and related stress-reactions are distinguished [Esch, 2002f; Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d]. Furthermore, stress implies a challenge (stimulus) that requires behavioral, psychological, and physiological changes (adaptations) to be successfully met, therefore using a state of hyperarousal for the initiation of necessary counteracting reactions [Esch & Stefano, 2002e; Esch et al. 2002c; McEwen, 2009; Stefano et al. 2005a]. This state of hyperarousal involves physiological mechanisms that are known as the stress or fight-or-flight response, a set of physiological changes that occur in stressful situations and that prepare the stressed organism either to fight or to flee. This state of alertness had first been described by Walter Cannon almost 100 years ago [Cannon, 1917; Cannon & Pereira 1924a; Cannon& Querido, 1924b]. Hans Selye, among others, has thereafter refined the physiological stress concept and its significance for biology and survival [Seyle, 1975; Seyle, 1973]. Modern concepts and recent studies have eventually associated the stress theory with human ailments and its neurobiological implications [Bakoula et al. 2009; Charmandari et al. 2005; Esch, 2002f; Esch, 2003d; Esch & Stefano, 2007b; Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d; Gould et al. 1997; Gold et al. 2005; McEwen, 1998; McEwen, 2008; McEwen, 2009; Meyer, 2001; Sapolsky, 2003; Sapolsky, 2004; Stefano et al. 2005a; Stefano et al. 2008c].

Stress occurs when we meet a sudden challenge and are forced to (re-) act in order to survive, or, less dramatically, to endure. When a zebra unexpectedly meets a lion, its physiology turns towards alarm, i.e., fight or flight (or eventually 'freeze', when the challenge is simply overwhelming, implying a physiological black out) [Esch, 2008a; Sapolsky, 2004]. Every bodily or mental activity is now scanned for the usefulness or deleteriousness in responding to the challenge, the stressor. Beneficial mechanisms will be enforced, others shut-down. This is natural and, at times, helpful, though exceptional. Following a successful escape or fight, the body naturally recovers, the mind relaxes [Esch et al. 2003b; Stefano et al. 2006]. Autoregulatory messengers and signalling molecules effortlessly enable this rebound or recreational state [Esch et al. 2009a; Salamon et al. 2006; Stefano et al. 2005d]. However, problems may occur when stress endures too long, is too massive or the physiology not fitted to fight a par-

ticular stressor [Esch, 2003d; Esch & Stefano, 2002e; Esch et al. 2002c; Stefano & Esch, 2005b; Stefano et al. 2005d]. Or when enough time for recovery is not allowed. Additionally, on an organic level, the biochemical response machinery that may turn off a stress response may be damaged [Fricchione et al. 1997]. And this seems to be a real human dilemma: equipped with the very same stress response mechanisms that the zebra fortunately possesses, we usually don't have to oppose life-threats in forms of lions or other external enemies in our daily life [Esch, 2002f; Esch, 2003d]. And so we start to think about the stresses and dangers in the future, the stressors and potentially stressful situations that might come, or the things that we encountered in the past, regarded as stressful [Stefano et al. 2005a]. And furthermore, we may start to dwell about our potentially suboptimal coping and resistance capacities in the present, thereby diminishing these very same capacities, causing us self-inflicted stress and impairment of our defence, i.e., 'cognitive constipation' [Stefano et al. 2005a]. Finally, an originally useful and helpful mechanism may convert to become deleterious, and stress-related diseases consequently emerge [Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d]. This is the critical path that underlies much of modern stress and human stress-related diseases. The good news is that we not only possess the endogenous capacity to self-inflict stress and harm, i.e., self-harm, but also to self-manage it, reduce its impact, be self-efficacious and endogenously heal or prevent stress disorders via SM [Fricchione & Stefano, 2005].

What is stress management?

Single cells, even bacteria, already possess physiological stress-attenuating or 'SOS response' capabilities [Esch, 1999; Esch, 2003d; Giuliodori et al. 2007]. These get activated when cells are exposed to stressors and substantial threats, i.e., alarm signals [Esch, 1999; Foster, 2005; Galhardo et al. 2007]. In fact, these cellular places of flexibility and adaptation include actively induced genomic and gene expression alterations under stress to better 'cope' with it and improve the cellular environment ('survival of the fittest genes'), and this regulatory potential may be a critical requirement for biological development and evolution itself [Dusek et al. 2008b; Esch, 1999; Esch, 2003d, Foster, 2005; Galhardo et al. 2007; Giuliodori et al. 2007; Rossano 2007]. Clearly, stress has given rise to biological progress and survival, again pointing at the potentially positive 'character' and biological necessity of the stress phenomenon, including the autoregulatory ability to constructively work with it for the better of the individual, and the species in particular [Esch, 1999; Esch, 2002f; Esch, 2003d; Stefano et al. 2005a]. What is true for the single cell, i.e., that it has an endogenous 'creative' stress response potential, is also true for the whole organism, including man [Esch & Stefano 2007b; Stefano et al. 2005a; Stefano et al. 2008c]. Even more, in complex organisms (in comparison to bacteria) these stress response options are diversified and manifold, e.g., due to higher integrative states of the nervous system and, under healthy conditions, a finely tuned neurobiological balance, that is, the neurobiology of stress and SM [Esch & Stefano 2005a, Esch& Stefano 2005b; Stefano & Esch 2005c].

SM builds on innate self-healing capacities [Esch, 2008a; Stefano & Kream, 2008a; Stefano et al. 2005a; Stefano et al. 2008b; Stefano et al. 2008c]. Our physiology is prone to regress to balance, i.e., a physiological or biological regression to the mean, therefore involving a dynamic autoregulation that leads to homeostasis or, in case of a state of arousal necessary to reach the required dynamic balance, to allostasis [Esch, 1999; Esch, 2002f; Esch, 2003d; McEwen, 1998; McEwen, 2008; Stefano et al. 2005a; Stefano et a1., 2008c]. The character of the balance finally achieved or secured, whether it is called 'homeostasis' or 'allostasis', is beyond the scope of this paper, however, it is the dynamic and potential to always return to the aspired set-point that is of importance for our hypothesis on the innate and overlapping biological SM capabilities. Usually, this balance or set-point is reached via dynamic autoregulation, i.e., allostasis or allostatic stress response pathways [Esch, 1999; Esch, 2003d; Esch et al. 2003b; McEwen, 1998; Stefano et al. 2005a]. Clearly, at the bottom of this self-organisational capacity lies our evolutionarily conserved SM potential [Esch, 2002f; eSCh, 2003d; Rossano, 2007].

To medically or professionally reduce stress, we usually engage in activities that consist of one to all (or individual combinations) of the following strategies: a) behavorial adjustments under stress, including cognitive interventions and mental restructuring (cognitive behavioral therapy), b) exercise and bodily activities, c) relaxation techniques, d) nutrition or eating – or not eating/diet – and, in general, learning to induce naturally occurring positive chemical messengers in our body (***Fig. 1***). Included in this list is the engagement in, or existence of, sufficient ('positive') social support as well as the belief in 'something', i.e., spirituality or connectedness (***Fig. 1***). These columns of a professional medical SM have been thoroughly examined, meanwhile, and their general clinical value appears to be obvious (e.g., see [Astin et al. 2003; Benson & Casey, 2008; Blumenthal et al. 2005; Daubenmier et al. 2007; Dusek & Benson, 2009; Dusek et al. 2008a; Ernst et al. 2009; Esch, 2002f; Esch & Stefano 2007b; Esch et al. 2003b; Grossmann et al. 2004; Kabat-Zinn et al. 1998; Kabat-Zinn et al. 1992; Komaroff, 2001; Le Tourneau, 2003; Michalsen et al. 2005; Ornish, 1998; Richardson & Rothstein, 2008; Schulz et al. 2008; Stefano et al. 2005a]). For the aim of this work, we will now take a deeper look into the physiology and neurobiological implications of these different stress-altering tools and search for possible commonalties among them. Since all these techniques potentially reduce stress and are beneficial in decreasing stress-related ailments and diseases, and since stress is an almost uniform cellular, bodily and mental process to ensure survival in a threatening situation (as described above: challenge or fight-flight), our speculation is that similar or overlapping neurobiological patterns and processes underlie these endogenous stress-reducing, self-healing strategies. Furthermore,

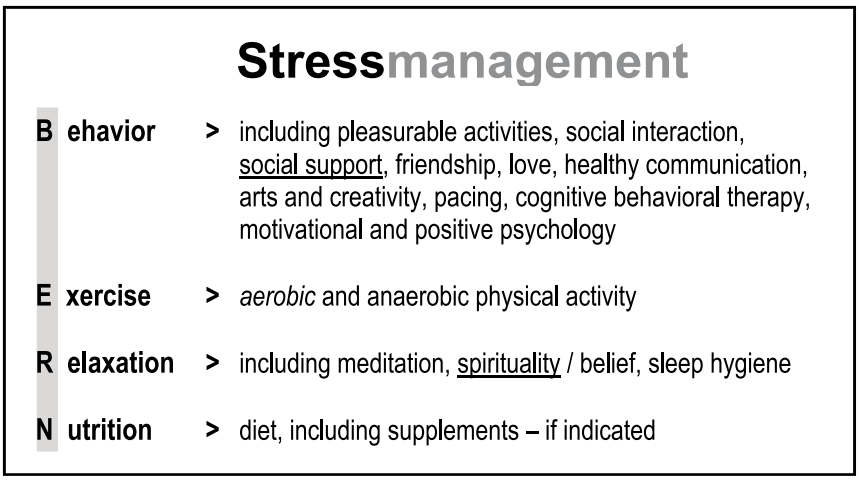

Figure 1: The BERN concept of stress management. The four columns of professional and integrative – i.e., multimodal – stress management programs such as BERN [Esch, 2008a; Esch & Stefano, 2007b; Esch et al. 2006b; Esch et al. 2009a; Stefano et al. 2005d] are a) behavior, b) exercise, c) relaxation, and d) nutrition; two further columns may be added (if not included, as above): social support and spirituality; cognitive behavioral interventions are critical ingredients i) of the behavioral column and ii) the underlying therapeutic model, i.e., mind-body medicine.

dopamine (DA), endogenous morphine (MO), endocannabinoids and nitric oxide (NO) signalling, as well as other related cellular and neurobiological messengers of autoregulation, may critically be involved [Stefano & Kream 2009].

The neurobiology of stress

Stress has an impact upon the immune, circulatory, and nervous systems [Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d]. However, the underlying physiology reveals high conformance, since the stress phenomenon and its impact are associated with common stress response pathways [Stefano et al. 2005a; Charmandari et al. 2005]. In fact, stress affects immunological [Esch et al. 2002a], cardiovascular [Esch et al. 2002b], and neurodegenerative or mental diseases/disorders [Esch et al. 2002d], and this may include both positive and negative aspects [Stefano et al. 2005a; Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d; Charmandari et al. 2005]. Stress can either exert ameliorating or deleterious effects, depending on a multitude of factors (e.g., individual, endogenous, or exogenous elements) [Esch, 2002f; Esch, 2003d; Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002c, Esch et al. 2002d; Esch et al. 2003b; Jones et al. 2001]. However, clinically, negative influences of stress upon health and disease processes seem to predominate [Esch, 2002f; Stefano et al. 2005a; Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d], which may especially be true in modern societies, where stress-related health issues and complaints almost have an epidemic character [Esch, 1999; Esch, 2002f; Esch, 2003d; Jones et al. 2001; Salavecz et al. 2009; Siegrist & Wahrendorf, 2009; Stefano et al. 2005a]. SM strategies, therefore, are of growing importance and acceptance since they address a "basic physiological process" in these societies and countries [Ernst et al. 2009; Esch, 2002f; Esch, 2003d; Le Tourneau, 2003; Richardson & Rothstein, 2008; Salavecz et al. 2009; Stefano et al. 2005a].

The brain is the central organ of stress and adaptation above normal tissue adaptive responses [McEwen, 2009]. When the brain perceives/senses an experience/stimulus as stressful, physiological and behavioral responses (stress responses) are initiated, leading to allostasis and adaptation, i.e., adaptive or allostatic stress responses [Esch 1999; Esch et al. 2003b; McEwen, 1998; Sterling & Eyer, 1988]. Thereby, the goal is to keep balance, self-organize and maintain autonomy under challenge – and ultimately to survive [Esch, 1999; Esch, 2003d]. When an organism chooses the right or successful strategy to fight a stressor and meet the challenge, a boost of rewarding (and stress-reducing) signalling molecules is released into the blood through the brain's reward and motivation centres, in the course of the evolving event or afterwards, to make the individual feel good, become positively motivated and reinforce (and memorize!) the beneficial behavior [Esch & Stefano, 2004c; Esch & Stefano, 2005a; Esch & Stefano, 2005b; Esch & Stefano 2007b; Mantione et al. 2008; Stefano & Esch, 2005c; Stefano et al. 2001a; Stefano et al. 2007a; Stefano et al. 2008c]. Successful adaptation is thus endogenously rewarded (see below). As a result of these ongoing processes of adaptation, over time, allostatic load can accumulate, and the overexposure to neural, endocrine, and immune stress mediators can have adverse effects on various organ systems, leading to the possible onset or progression of diseases [Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d; McEwen, 1998]. Hence, profound physiological and molecular connections between stress and various disease processes exist [Charmandari et al. 2005; Esch, 2003d; Stefano et al. 2005a]. Common pathophysiological pathways in stress-related diseases have been described [Esch & Stefano 2002e; Esch & Stefano, 2007b; Esch et al. 2002c; Esch et al. 2003a; Stefano et al. 2005a], and they critically involve stress hormone (e.g., cortisol, norepinephrin (NE)) and, in particular, NO activity (see below). Moreover, as noted earlier, stress may trigger the activation of a damaged or insufficient biochemical cascade designed to address such "normal" perturbations. In this scenario an individual may have trouble terminating this response, which, under these circumstances, will allow for a long and chronic response sine the terminating processes are not functioning or fully functional [Fricchione et al. 1997].

Two molecules that play a major role in the stress response are well-known. Each molecule represents one neurobiological 'arm' of the response, the hypo-

thalamic-pituitary-adrenal (HPA) axis on one side and the sympathoadrenal medullary (SAM) system on the other [Negrao et al. 2000]. The molecules are cortisol and NE/epinephrine [Negrao et al. 2000; Cannon, 1914; McCarty, 1996]. Corticotropin-releasing hormone (CRH) also belongs in this company of critical molecules, i.e., HPA axis [Charmandari et al. 2005; Esch et al. 2002a]. More recently, other molecules with a close connection to the stress neurobiology have been detected, e.g., melatonin and melanocyte-stimulating hormone [Brotto et al. 2001; Charmandari et al. 2005], vasopressin [Charmandari et al. 2005; Esch & Stefano, 2005a; Esch & Stefano, 2005b; Stefano & Esch, 2005c], oxytocin [Esch & Stefano, 2005a; Esch & Stefano 2005b; Stefano & Esch, 2000c], endocannabinoids [Esch, 2005c; Esch et al. 2006; Stefano, 2000e; Stefano et al. 2003], and endorphins [Charmandari et al. 2005; Esch & Stefano, 2004c; Stefano et al. 2005d; Stefano et al. 2001a]. Furthermore, a connection of NO with the stress response has been demonstrated, since this signalling molecule is part of the stress physiology and related disease processes: NO is involved in immunological, cardiovascular, and neurodegenerative diseases/mental disorders, associated with stress [Cordellini & Vassilieff, 1998; Esch et al. 2002c; Esch et al. 2003a; Gumusel et al. 2001; Mantione et al. 2005; Stefano & Esch, 2005b; Stefano et al. 2001a; Stefano et al. 2001b; Stefano et al. 2005d; Stefano et al. 2008b; Stefano et al. 2009a; Zhu et al. 2004; Zhu et al. 2005b]. It represents a 'double-edged sword', since small quantities produced by constitutive enzymes may predominantly mediate physiological or beneficial effects, whereas the expression of inducible NO synthases may lead to larger quantities of NO, a situation that may be associated with cytotoxic and detrimental biological effects of NO [Esch et al. 2002c; Esch et al. 2003a; Stefano et al. 2005a]. These latter NO effects, in particular, seem to be associated with stress and the negative side-effects of it.

In addition, stress effects and (patho-) physiological consequences are potentially 'transferred' not only within the individual (e.g., systemic interactions between mind, brain and body [Esch, 2008a; Komaroff, 2001; Sapolsky, 2004; Stefano et al. 2001a; Stefano et al. 2005a], but also towards other 'neighbouring' cells and organisms, even those initially not under stress, e.g., by the means of verbal/non-verbal communication or the exchange of molecular and physical information [Esch, 1999; Esch, 2003d; van Wijk et al. 2008a; van Wijk et al. 2008b; Wiegant et al. 1996]. Furthermore, stress mediation and specific impact of stress hormone activity may be carried over biologically and conserved beyond generation borders, since parents and their offspring show stress response commonalities and physiological/neurobiological as well as stress behavioral coupling [Bakoula et al. 2009; Charmandari et al. 2005; Chin et al. 2009; Moles et al. 2004]. This transfer of stress consequences via neurobiological, physical, or chemical coupling can even include genetic alterations, and these effects may be relatively stable [Chin et al. 2009; Esch, 1999; Meyer et al. 2001; Wiegant et al. 1996].

Another important element of stressful stimulation may be the duration or time component of the noxious or challenging stimulus [Esch & Stefano, 2007b; Fricchione & Stefano, 1994]. A brief physical or mental 'assault' may allow an organism to deal with both an appraised or perceived stress through various detailed allostatic compensatory mechanisms [Stefano et al. 2005d]. If the situation were to continue chronically, the organism might become vulnerable, susceptible to the negative aspects of the stress response, such as in the case of prolonged immune down-regulation [Esch et al. 2002a, Stefano & Scharrer, 1994; Stefano et al. 1995c; Stefano et al. 1996a; Stefano et al. 1996b; Stefano et al. 2000d]. Moreover, our physiological and psychological stress response systems plainly function, or were designed to do so, over the short-term, i.e., fight or flight, not for prolonged periods of time [Esch, 2000f]. Given the signal molecule commonalties and similarities found in diverse organisms during the course of evolution, not to mention the common design of animal nervous systems regardless of phyla [Salzet & Stefano, 1997b; Salzet & Stefano, 1997c; Salzet et al. 1997a; Stefano et al. 1998a; Stefano et al. 1998b; Stefano et al. 1998c; Stefano et al. 2000b; Stefano et al. 2002; Stefano et al. 2005d; Stefano et al. 2008b; Stefano et al. 2008c], it is not surprising to learn that they also similarly exhibit stress responses, which appear to be the same and rapid in implementation [Esch, 2003d; Stefano et al. 2002].

Stress, as described above, is natural and at times very helpful in regard to survival strategies. However, the underlying physiology can also lead to detrimental effects. As the stress response is normal, so is the innate physiology that follows or terminates activated stress pathways, once initiated in a challenging situation [Esch, 2008b; Esch & Stefano, 2007b]. Under normal conditions, these SM pathways (see below) follow the same neurobiological roads that the stress mechanisms use, e.g., brain's limbic areas and the neuronal stress axes. For activating this innate autoregulatory healing potential, the brain even falls back on some of the very same molecules that account for the initial stress response [Esch & Stefano, 2004c; Esch et al. 2002c; Mantione et al. 2008; Stefano & Kream, 2008a; Stefano et al. 2008b]. As an example, one can look at what we called the 'anticipatory stress response', or 'love response' [Esch & Stefano, 2005a; Esch & Stefano, 2005b; Stefano & Esch, 2005c; Stefano et al. 2008c]: in the beginning of an ultimately relaxing and pleasurable experience, such as falling or being in love, or executing a relaxation exercise, the body occasionally goes into a short period of stress and physiological activation, e.g., to screen the environment for potential challenges or threats, thereby ensuring that it is safe to relax [Stefano et al. 2008c], or to love [Esch & Stefano, 2005b]. Then, the physiology turns into an innate stress reduction, i.e., endogenous SM, only by activating additional stress response mediators or lowering concentrations of some stress molecules while enhancing others [Esch & Stefano, 2002e; Esch & Stefano, 2005a; Esch & Stefano, 2005b; Esch & Stefano, 2007b; Esch et al. 2002c; Esch et al. 2003b; Esch et al. 2004a; Esch et al. 2004b; Esch et al. 2006b; Salamon et al. 2006; Stefano & Esch, 2005c; Stefano et al. 2003; Stefano et al. 2005a; Stefano et al. 2005d; Stefano et al. 2006; Stefano et al. 2008c].

Chronic stress can impact many physiological systems given their reliance on common biochemical

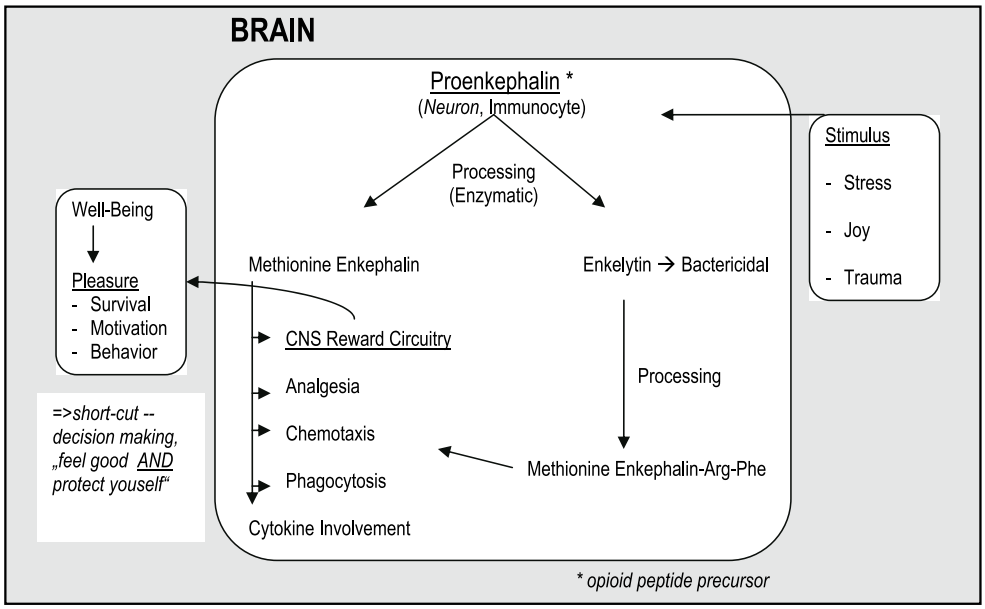

Figure 2: Opioid peptides as stress hormones. Stress triggers a release of proenkephalin that gets processed into enkelytin and Met-enkephalin. This step characterizes opioid peptides as stress hormones at the border to stress autoregulation, i.e., endogenous stress reduction, since they have the functions of a 'double-edged sword': in part, the opioid peptides/endorphins enable the stressed organism to stay active beyond the normal or physiological duration of a stress cycle (e.g., ca. 90 minutes max. in humans), by signalling the individual to keep up with the stress activity (because it might be biologically necessary), while reducing pain and other physiological companions of a prolonged stress response. In this case, the activated immune response and defence is upheld, typical signs of stress response activity prevail. However, the opioid peptides already prepare for the relaxing and recovering part of stress, i.e., stress management, since motivation and behavioral adjustments are positively influenced; references: [Fricchione & Stefano, 1994; Stefano & Scharrer, 1994; Stefano & Kream, 2008a; Stefano et al. 1996b; Stefano et al. 1998a; Stefano et al. 2001a; Stefano et al. 2005a; Stefano et al. 2005d].

processes [Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d]. In part, the reason for this may be that at the core of many disorders one may find a proinflammatory situation that manifests itself in diverse tissues, differently masking the commonality [Esch & Stefano, 2002e; Stefano et al. 2005d]. However, it may be the ability to induce relaxation that breaks the negative impact of chronic stress [Esch et al. 2003b; Stefano et al. 2008c]. Taken together, the acute stress response is highly protective since it is designed in animals to meet an immediate challenge. Yet, over time, initially positive effects can turn into the opposite, i.e., chronic stress. The underlying physiology of stress critically involves neurobiological pathways and circuitries, such as the central neuronal stress axes or limbic reward and motivation circuits. Stress mediators and other effectors that build the neurobiological and molecular basis of these stress mechanisms are, besides the classical stress hormones NE and cortisol, for example, DA, the endocannabinoids and endorphins, oxytocin, vasopressin, NO and, eventually, endogenous MO [Bakoula et al. 2009; Charmandari et al. 2005; Esch & Stefano, 2005b; Gold et al. 2005; Gould et al. 1997; Kream et al. 2009; McEwen, 1998; McEwen, 2008; Meyer et al. 2001; Sapolsky, 2003; Sapolsky, 2004; Stefano & Kream, 2009c; Stefano et al. 2005a; Stefano et al. 2008c].

The general 'idea' of the stress neurobiology may be that a stressed organism gets immediate energy supply and physiological activation for fighting, or taking flight, while other systems of minor importance for this primary goal (or even negatively interfering with it) get shut-down, i.e., down-regulation [Stefano et al. 2005a]. This differential preference for physiological activation may even extend into mitochondrial regulation, ultimately altering energy metabolism [Kream & Stefano, 2009b]. For example, the experience of pain may call the attention of a 'stressed' individual (e.g., during a fight) towards the source of this noxious sensation. However, when the fight is not over, that is, the challenging problem not solved, it might not be a good idea to put too much effort and immediate attention into the investigation of the ache, which makes it thus necessary to have endogenous pain relieving stress mediators 'at hand' to become released during prolonged stress. This may be a critical function of the endorphins in stress, as they are endogenous stress effectors and, additionally, at the border towards relaxation [Esch & Stefano, 2007b; Salamon et al. 2006], especially cognitively, as they appear in a subsequent phase of the stress cycle, consecutively delayed in comparison to the initial stress hormones (***Fig. 2*** and ***3***).

Endorphins are immunobiologically defence-active, as they act as antibacterial substances themselves and also trigger proinflammation beyond that [Esch et al. 2002a; Esch & Stefano, 2002e; Stefano et al. 2001a; Stefano et al. 2005a; Stefano et al. 2005d]. After successfully overcoming the initial threat, the system, under normal circumstances, endogenously recovers by involving another set – or a different 'orchestration' – of autoregulatory molecules, which addition-

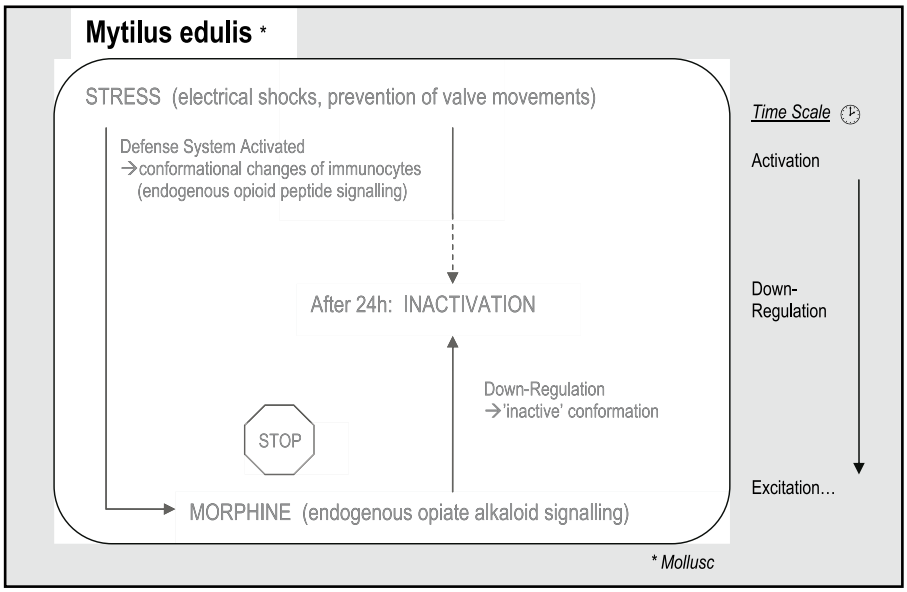

Figure 3: Endogenous stress response management. Stress leads to an activation of opioid peptide influences on the immune system of the mollusc Mytulis edulis [Hughes et al. 1990; Stefano et al. 1990]. Over time, however, the activity gets down-regulated by the release of opiate alkaloids, e.g., endogenous morphine, thereby ending the stress response cycle. When the system goes back to complete normal function, by also terminating the endogenous stress management or relaxation part (that is, the morphine-related down-regulatory phase), a rebound from down-regulation may occur, i.e., excitation; further references [Stefano et al. 1998b; Stefano et al. 1998c; Stefano et al. 2002].

ally or consequently reward the chosen behavior (i.e., strategy), thereby also improving the memorization of it, further recovering the initially blocked systems and energy stores, thus, finally, bringing the system back to normal under inclusion of neurobiological, physiological, and even behavorial adaptations (***Fig. 3*** and ***4***). The organism gets the good feeling of 'having done the right thing', although, in the immediate phase of the acute stress response, the conscious cognitive dwelling upon the stressor/challenge and its possible impact was blocked, i.e., rational short-cut [Esch & Stefano, 2004c; Esch et al. 2004a; Esch et al. 2004b; Stefano et al. 2005a]. Yet, the innate 'feeling good part' in the late phase of a successfully terminated stress response leads us to the endogenous autoregulation of stress and its common pathways: the neurobiology of SM.

Neurobiology of stress management

In the above section, we looked at underlying principles of the stress response and depicted some of its neurobiological key players, and finally brought those in line with the idea of an endogenous autoregulation, i.e., physiological self-care and SM. In the following section of this report, we will focus upon the neurobiological commonalties that can be found between the columns of a professional SM regimen (***Fig. 1***: BERN), particularly with regard to the molecular effectors. For our analysis, we will have a closer look at endogenous dopaminergic and particularly morphinergic signalling, since this latter opiate alkaloid has only recently been found in human tissues (e.g., [Atmanene et al. 2009; Bilfinger et al. 2002; Boettcher et al. 2005; Fricchione et al. 2008; Olsen et al. 2005; Poeaknapo, 2005; Poeaknapo et al. 2004; Stefano & Kream, 2009c; Zhu et al. 2005a; Zhu et al. 2007]) and linked to stress regulation (***Fig. 4***). Indeed, the catecholamine pathway may have arisen from endogenous MO biosynthesis, coupling these signalling processes in an even more intimate relationship as also made evident by common enzymes in the synthesis of these chemical messengers [Mantione et al. 2008; Neri et al. 2008; Stefano & Kream, 2007b; Stefano & Kream, 2009c]. The results that we now report have, to our knowledge, not been put into relation to each other so far, as they have not been linked to an overall neurobiological principle, i.e., stress autoregulation.

Behavior

There exists a high congruency between the different techniques and approaches towards behavioral stress reduction (***Fig. 1***) when it comes to underlying neurobiological pathways (see below). Again, we find the same molecular key players as in stress. In fact, the neurobiology of behavioral SM seems to be imbedded in the brain's pleasure, motivation and reward circuitries [Stefano & Kream, 2007b; Stefano & Kream, 2009c].

Modern science begins to understand pleasure as a potential component of salutogenesis [Esch & Stefano, 2004c]. Thereby, pleasure is described as a state or feeling of happiness and satisfaction resulting from an experience that one enjoys. We and others examined the neurobiological factors underlying these reward and pleasure processes and why they potentially possess a stress-reducing capability via behavioral adjustments, e.g., behavioral SM [Berridge & Kringelbach, 2008; Esch & Stefano, 2004c;

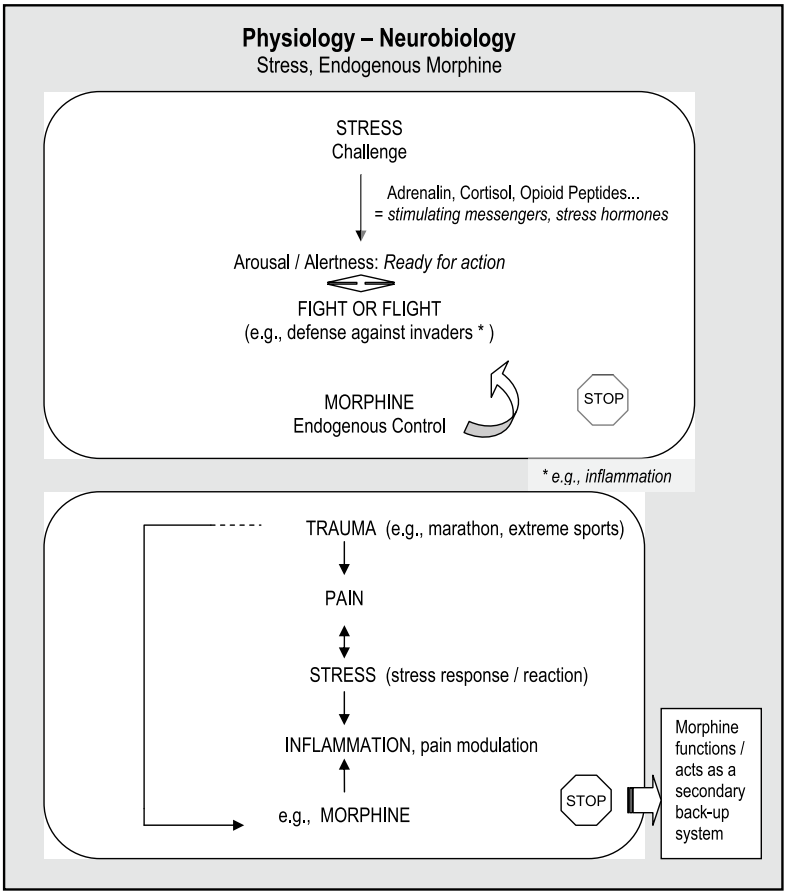

Figure 4: Stress and morphine autoregulation. The general neurobiological principle of autoregulatory stress response mechanisms, i.e., endogenous stress management, is to terminate the initial stress response and recover the systems, i.e., secondary back-up; references: [Cannon, 1914; Esch, 2008b; Esch & Stefano, 2002e; Esch & Stefano, 2007b; Esch et al. 2002a; Esch et al. 2009a; Kream et al. 2009; McCarty & Gold, 1996; Salamon et al. 2006; Stefano et al. 1995c; Stefano et al. 1996b; Stefano et al. 2005d].

Esch & Stefano, 2005b; Esch et al. 2004b; Salamon et al. 2005; Stefano & Esch, 2005c; Zhu et al. 2004]. This stress-pleasure-self-regulation, as the name implies, combines externally stimulating or challenging activities with internal or endogenous brain processing, therefore involving dopaminergic signalling as a core pathway [Berridge & Kringelbach, 2008; Berridge & Robinson, 1998; Esch & Stefano, 2004c; Esch et al. 2004b]. Furthermore, the regulation of attachment behaviors, critical for positive social support, as this is a major stress-reducing activity, involves endogenous opioid and opiate as well as endocannabinoid signalling and, via direct receptor coupling, NO autoregulation [Esch et al. 2002c; Esch et al. 2006b; Mahler et al. 2007; Mantione et al. 2008; Moles et al. 2004; Salamon et al. 2005; Stefano, 2000e; Stefano et al. 2001a; Stefano et al. 2003; Stefano et al. 2007a]. Oxytocin, vasopressin and even serotonin, as well as some stress hormones (e.g., stress catecholamines), work through this same positive behavioral and motivational mechanism on stress reduction and health gains [Breard et al. 2007; Chanrion et al. 2007; Esch et al. 2002d; Esch & Stefano, 2005b; Stefano & Esch, 2005c; Stefano et al. 2008c; Salamon et al. 2005; Umathe et al. 2009; Yu et al. 2008]. The underlying neurobiological principle, though 'deep', appears to be rather simple: Experiences, activities and behaviors are constantly and automatically self-evaluated for their health benefits and stress reduction potential, i.e., stress relief (***Fig. 5***), and then rewarded by an autoregulatory release of endogenous 'pleasure molecules', subsequently enhancing the biological imprint and memory of the original behavior as positive and beneficial (e.g., low stress, wellness), if given, yet again providing a positive or appetitive motivation to repeat this behavior, at least after the appetence for that specific activity has been restored [Esch & Stefano, 2004c]. The down-side of this neurobiological circuit is the possibility of addiction for extremely rewarding activities and behaviors, i.e., motivational toxicity [Esch & Stefano, 2004c; Mantione et al. 2008; Stefano et al. 2007a]. Importantly, these common signal molecule pathways, i.e., DA, MO, work in a similar manner as found in addiction influenced pathways, e.g., nicotine, alcohol, cocaine [Stefano et al. 2007a].

Pleasurable behaviors can be highly stress-reducing and/or -protective. This seems to be true for almost every positive psychology or cognitive behavioral intervention with the aim of improving health [Berridge & Kringelbach, 2008; Esch & Stefano, 2004c; Esch et al. 2004b; Esch & Stefano, 2005b; Lee Duckworth et al. 2005; Siegel, 2009; Sin & Lyubomirsky, 2009], including arts, creativity, and music (e.g., musical healing [Esch, 2003c; Esch, 2003e; Esch, 2009b]). The reason for this common healing or stress therapeutic potential may be that the said behaviors involve the same hardware, that is, the brain's limbic reward and pleasure pathways, for realizing their beneficial effects [Berridge & Kringelbach, 2008]. In particular, frontal and prefrontal affective regions of the brain are crucial for the positive validation of individual experiences and the consecutive self-regulatory stress reduction and reward, additionally, by decreasing the amygdaloidal arousal and fearful resistance that sometimes accompanies stressful encounters, or the

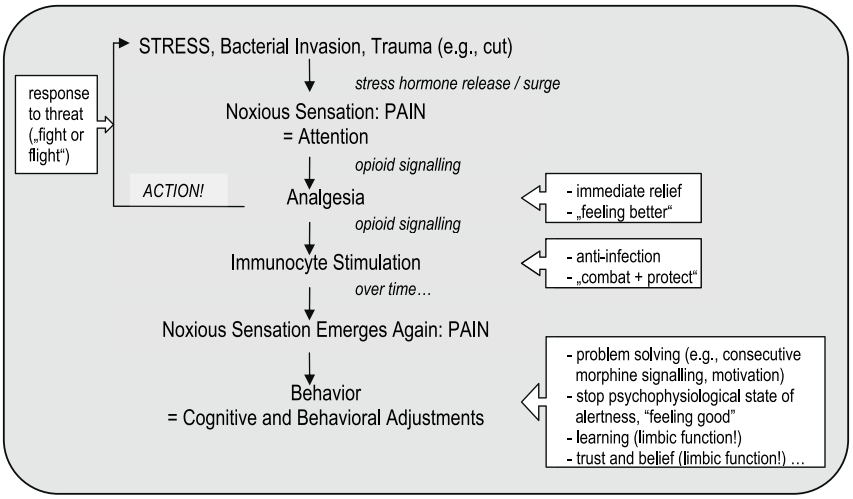

Figure 5: The neurobiology of stress management – behavioral adjustments. In addition to molecular changes during the stress/stress management cycle of autoregulation, behavioral adjustments are conducted, then eventually evaluated and finally learned (e.g., memorized via hippocampal/limbic activity in the brain), when regarded as beneficial. This molecular-behavioral interaction marks the integration of cognitive behavioral changes as the final result of a physiological stress cascade; references: [Esch & Stefano, 2004c; Esch & Stefano, 2007b; Esch et al. 2004b; Esch et al. 2009a; McEwen, 2009; Negrao et al. 2000; Sapolsky, 2003; Stefano & Kream, 2008a; Stefano et al. 2005a; Sterling & Eyer, 1988].

emotional (hyper-) alertness that particularly comes with unexpected stressful, unfamiliar behaviors or situations [Esch, 2003d; Esch et al. 2002d; Salamon et al. 2005; Stefano et al. 2008c]. The frontal parts of the brain and, accordingly, the anterior limbic proportions (the orbitofrontal cortex, for example, or the dorsolateral prefrontal regions) seem to stabilize positive mood, i.e., affectional stress hardiness, resistance or affective resilience [Berridge & Kringelbach, 2008; Davidson et al. 2003; Esch & Stefano, 2004c; Esch et al. 2004a; Esch et al. 2004b]. Other regions of critical importance are the nucleus accumbens, anterior cingulate, the ventral tegmental area, ventral pallidum, or parts of the insular and brainstem [Berridge, 2003; Berridge & Kringelbach, 2008; Esch & Stefano, 2004c; Esch et al. 2004b]. Many of these regions are functionally and anatomically shared between humans and other animals (***Fig. 3*** and ***5***), since the morphinergic and dopaminergic mesostriatal, mesocortical and especially the mesolimbic pathways and projections, found in many species, link the different hedonic hotspots and motivation areas into an integrated reward system [Berridge & Kringelbach, 2008; Esch & Stefano, 2004c; Kringelbach, 2005; Panksepp, 2007; Smith & Berridge, 2007; Stefano et al. 2001a].

Taken together, hedonic or pleasurable behaviors are important 'ingredients' of medical SM interventions (***Fig. 1***). Prima facie, they appear to be accidently compiled and not behaviorally or even physiologically linked together, making them possibly appear not forceful. However, they are clinically effective. We surmise that this may be due to their common and powerful neurobiological pathways for self-regulation and self-efficacy, which underlie numerous health behaviors. In the end, the stress-ameliorating potential of these behaviors (that could even include spiritual practices or engagement in 'connectedness rituals', etc. – ***Fig. 1***) is related to their general pleasure and happiness potential, which may turn off rational behaviors that are dwelled on for longer than necessary periods of time. This potential, and the neuroanatomical 'hardware' behind it, is largely shared among the various stress-reducing behaviors.

Exercise

'Mens sana in corpore sano' (a healthy mind in a healthy body), or more precisely, 'orandum est, ut sit mens sana in corpore sano' by Juvenal means that one has to beg and care for a healthy body for that is the precondition of a healthy mind and a balanced function of cognition, and possibly, vice versa. Thus, the idea of an interconnection between mind and body with reference to health, cognition, and exercise is almost 2000 years old. Physical activity, particularly aerobic exercise, can improve a number of aspects of cognition and bodily performance [Hillmann et al. 2008; Stroth et al. 2009; Voelcker-Rehage et al. 2006]. Every dynamic physical activity, but not static tasks or sedentary lifestyles, leads to a marked increase of regional cerebral blood flow [Herholz et al. 1987; Hollmann & Strueder, 1996; Hollmann & Strueder, 2000a; Hollmann & Strueder, 2000b]. Lack of physical activity, especially among children, is a major cause of obesity and the early onset, and consecutive aggravation in adult life, of many diseases, e.g., cardiovascular or metabolic [Ben-Sefer, 2009; Hillmann et al. 2008]. However, there is substantial evidence mounting up that suggests exercise not only to be highly recommendable for keeping and enhancing physical health, but also to improve academic and mental performance – 'running makes smart' [Hillmann et al. 2008; Stroth et al. 2009; van Praag et al. 2005; Voelcker-Rehage et al. 2006]. We suggest that this effect may, in parts, be attributed to the endogenous stress reduction and protection potential, and a related neurobiological involvement of limbic portions of the brain as well as the underlying molecular pathways, already displayed above. Within this section, we further scrutinize this hypothesis.

Physical activity is a lifestyle factor that leads to increased health and stress hardiness throughout life [Erickson & Kramer, 2008; Esch, 2002f; Hillmann et al. 2008; Hollmann & Strueder, 1996; Hollmann & Strueder, 2000a; Hollmann & Strueder, 2000b; Voelcker-Rehage et al. 2006]. It's good to start early and not give up this practice while growing up. However, even the physical and mental decline of the elderly is not completely inherent or predestined, only reliant on genes

or 'fate', but instead, partly reversible. Yet, these age-dependent processes can be delayed, some prevented, compensated, or even reversed, 'just' by starting to get active again, during old age [Erickson & Kramer, 2008; Hollmann & Strueder, 2000b; Lazar et al. 2005; van Praag et al. 2005; Voelcker-Rehage et al. 2006]. The critical aspect for this potential is the life-long ability of the brain to adjust and adapt, actually on the molecular level, and this capacity can be trained, i.e., neuroplasticity [Lazar et al. 2005; Voelcker-Rehage et al. 2006]. A very capable training stimulus therefore seems to be mild and manageable mental stimulation, e.g., stress or SM, or mild aerobic exercise [Erickson & Kramer, 2008; Hollmann & Strueder, 1996; Hollmann & Strueder, 2000b; Lazar et al. 2005; van Praag et al. 2005]. This neuroplastic effect of exercise therapy also works with stroke patients, demonstrating it as an effective life strategy [Gertz et al. 2006; Wolf et al. 2006].

Appropriate lifestyle or purposeful activity interventions can positively influence the reserve capacity of aging humans and the aging process itself, particularly with regard to physiological development, cognitive performance, longevity, as well as the onset and course of chronic diseases [Hollmann & Strueder, 2000a; Voelcker-Rehage et al. 2006]. Cognitive development and state are plastic, i.e., flexible, facilitated by positive behaviors (see above) and activity, cognitive as well as physical [Voelcker-Rehage et al. 2006]. Clearly, body and mind are interconnected [Esch, 2008a; Hollmann & Strueder, 2000b]. For using this capacity, it is important to train cognitive and physical flexibility, likewise, which seems to be true for SM as well [Esch, 2003d; Stefano et al. 2005a; Stroth et al. 2009; van Donkelaar et al. 2009]. However, the effect of physical activity on cognitive function, particularly – but not exclusively – in the elderly, turns up to be eminently impressive [Erickson & Kramer, 2008; Voelcker-Rehage et al. 2006; van Praag et al. 2005].

Physical exercise improves learning. Obviously, this effect is based upon the enhancement of neurogenesis in the hippocampus through bodily activity, a brain area critical for learning and memory, particularly with regard to the declarative long-term memory, and it is part of the limbic brain [Esch et al. 2002d; Pollak et al. 2008; van Praag et al. 2005; van Praag et al. 2008]. Clearly, there exists a positive neurobiological correlation between running and neurogenesis [van Praag et al. 2008]. Interestingly, the hippocampus is also extremely sensitive to stress, since psychosocial or mental stress, in particular, tend to deteriorate neurons in the hippocampus, leading to accelerated neurodegeneration and possibly dementia [Esch et al. 2002d; Guarna et al. 2004; McEwen, 2001]. As with stress, aging causes hippocampal decline [van Praag et al. 2005]. This negative effect of stress – and aging – is potentially counteracted by exercise. In fact, stress has a direct impact upon the production/release of brain-derived neurotrophic factor (BDNF), which itself is strongly linked to the serotonin system and plays an essential role in mood and memory processes [Pollak et al. 2008; van Donkelaar et al. 2009]. More precisely, stress decreases BDNF levels, particularly in the prefrontal cortex where the working memory is located [van Donkelaar et al. 2009]. Moreover, brain tryptophan levels and serotonin metabolism correlated positively with BDNF in both prefrontal cortex and hippocampus in a recent stress-brain-neurobiology study, again highlighting the close interconnection and commonality between the underlying signalling systems [van Donkelaar et al. 2009]. This appears to be also true for the stress-memory-opioid/opiate/endogenous MO connection (see below, and [Esch et al. 2002d; Guarna et al. 2004]), although a rather complex matter and not fully understood yet.

Stress alters memory performance, and MO interacts with this phenomenon, be it as a primary target of stress-related memory alteration or, supposedly, as a secondary back-up player, i.e., autoregulation, following a stress-related 'narrowing' of the memory focus and attention concentration with the putative goal of deleting every memory input that, in the moment of fight or flight (acute stress), would negatively interfere and not serve the hoped for positive outcome for the fighting individual: while stressed, new or other working memory contents are badly learned, that is, acquired and consolidated [Esch et al. 2002d; Guarna et al. 2004; Pollak et al. 2008]. However, it seems to be biologically essential to keep the 'idea' of a successful strategy that helped to fight the stressor in mind, and somehow accessible afterwards, so that after the fight is over, this successful strategy can become endogenously evaluated and, if positive, memorized (learned). MO seems to play a critical role in this process, for example, as a recovery or secondary back-up molecule (***Fig. 4*** and ***6***).

As stated above, exercise enhances learning, function and neurogenesis in the hippocampus and the prefrontal cortex, e.g., via BDNF, and this cascade is negatively influenced by stress [Erickson & Kramer, 2008; McEwen, 2001; Pollak et a., 2008; van Donkelaar et al. 2009; van Praag, 2008]. In fact, stress and physical activity are counter players [Esch, 2002f; Esch et al. 2003b; McEwen, 1998; McEwen, 2008; Sapolsky, 2004; Stefano et al. 2005a], and stress reduction through exercise not only improves memory functions, hippocampal neurogenesis and BDNF levels, but also mood, quality of life, and overall well-being [Boecker et al. 2008; Esch, 2002f; Esch & Stefano, 2004c; Esch et al. 2002d; Esch et al. 2004b; Pollak et al. 2008]. However, this seems to apply only to moderate exercise, since prolonged and strenuous physical activity, for example, can itself cause stress and proinflammation [Esch & Stefano, 2002e; Esch et al. 2002c; Hollmann & Strueder, 2000b; Rojas Vega et al. 2006b; Rojas Vega et al. 2006a; Stefano et al. 2001c].

Besides the prefrontal or orbitofrontal and hippocampal areas of the brain, there are other regions that also seem to be of importance in the neurobiological SM-exercise-cognition relationship, e.g., temporal cortex, bilateral insula and parainsular cortex, as well as temporoparietal regions, the amygdala and anterior cingulate, yet again suggesting region-specific effects in frontolimbic brain areas that are also involved in the processing of affective states and mood [Boecker et al. 2008; Erickson & Kramer, 2008; Hollmann & Strueder, 2000a; Pollak et al. 2008]. Hence, stress reduction, e.g., through exercise, has been shown to involve serotoninergic, and especially dopa-

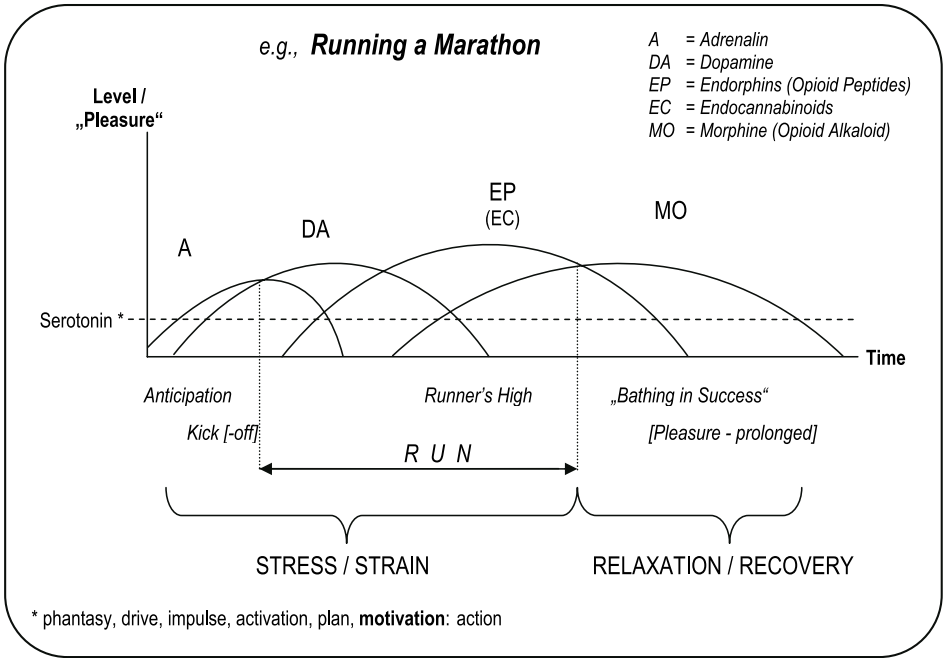

Figure 6: The neurobiology of stress management – running a marathon. Occurrence of autoregulatory signalling molecules over time in enduring and challenging tasks, including a subsequent recovery phase, where the system regenerates and the benefits of a successful 'fight or flight' are imprinted and actually gained; speculative, schematic draft: time/period around a planned marathon run; references: [Berridge & Robinson, 1998; Boecker et al. 2008; Breard et al. 2007; Chanrion et al. 2007; Charmandari et al. 2005; Esch, 2005c; Esch & Stefano, 2007b; Esch et al. 2006b; Hillmann et al. 2008; Hollmann & Strueder, 2000a; Hollmann & Strueder, 2000b; Mantione et al. 2007; Meyer et al. 2001; Neri et al. 2008; Pollak et al. 2008; Sapolsky, 2004; Stefano et al. 2003; Stefano et al. 2005a; Stroth et al. 2009; van Praag et al. 2008].

minergic and neuropeptidergic signalling in the associated brain regions [Pollak *et al.* 2008; Stroth *et al.* 2009]. DA, for example, seems to be of particular interest here for spatial memory, concentration and positive mood, as well as for the general effectiveness of the brain performance, or the reestablishment and safekeeping of a normal brain function in the course, e.g., of exhausting (cognitive) tasks [Stroth et al. 2009]. Thus, DA-enhancing exercises and activities appear to be suitable means to balance stress on the neurobiological level. Moreover, these various signalling molecules have to be finely tuned in challenging tasks, especially while prolonged or enduring, as suggested in ***Fig. 6***.

The chronology and sequence of stress or stress-reducing hormone and neurotransmitter release during exercise not only depends on the actual point in time of the release, but also on the concentration and half-life, i.e., kinetic pattern, of the hormone into question. For example, BDNF and cortisol differ in that they both are produced, elevated through rampant or strenuous and exhausting exercise, however, BDNF returns to base levels instantly after the exercise challenge is over, while cortisol recovers slower [Rojas Vega et al. 2006b]. Furthermore, the type of exercise is essential, as noted before, with aerobic and moderate exercise being optimally suited, in fact crucial, for molecular stress reduction and health (***Fig. 1***; also see [Hollmann & Strueder, 2000a; Hollmann & Strueder, 2000b; Stefano et al. 2001c; Stroth et al. 2009]).

Long-term exercise, such as distant running, can lead to an euphoric state that is sometimes called 'runner's high' (***Fig. 6***), enabling the runner to proceed with the task, though exhausting. The neurochemical correlates of this exercise-induced positive mood change critically build on opioidergic mechanisms in the brain, that is, opioid receptor activation, preferentially in prefrontal and limbic or paralimbic brain structures [Boecker et al. 2008]. The runner's high phenomenon is an obvious result of autoregulatory opioid signalling. The opioid peptides (endorphins) beta-endorphin and Met-enkephalin with its precursor proenkephalin originate from the anterior pituitary, where proopiomelanocortin (POMC) is produced, again showing the connection between this signalling system and the central stress axes, as illustrated. Interestingly, prolactin is also enhanced during and post-exercise, however, this latter hormone is a partial DA inhibitor that comes consecutively (i.e., delayed) after DA release in the stress-exercise sequence was initiated [Rojas Vega et al. 2006a], comparable to the endorphins (***Fig. 6***). Prolactin also originates from the anterior pituitary. The more prolactin builds up in an exercise, e.g., sexual activity, the deeper the relaxation and satisfaction later [Rojas Vega et al. 2006a], comparable to the postulated DA-MO sequence (***Fig. 6*** and [Esch & Stefano, 2005a; Esch & Stefano, 2005b; Stefano & Esch, 2005c; Stefano et al. 2007a]). In other words, the greater the stress (in combination with physical activity and exhaustion), the deeper the relief and relaxation, i.e., endogenous stress reduction and reward (the 'I did it' component), when successfully solving and overcoming the stressful challenge.

Finally, since DA, endocannabinoids and MO (and even serotonin – see above) exert their effects, in part, via NO release, it is not surprising to find substantial constitutive NO activity in exercise [Gertz et al. 2006; Mantione et al. 2007; Stefano et al. 2001c]. We surmise that this potentially protective neurobiological signalling molecule plays the role of an effector for many of the observed phenomena of autoregulation (***Fig. 7***). For example, positive results with exercise therapy in stroke patients are abolished by the inhibition of NO signalling [Gertz et al. 2006]. Moreover,

NO counteracts NE, that is, cellular stress, on the neuronal level, thereby explaining a self-regulatory anti-stress capacity of NO-enhancing activities [Esch et al. 2002c; Esch et al. 2003a; Stefano et al. 2001a]. Taken together, we hypothesize that exercise induces autoregulatory stress reduction via limbic pleasure and reward pathways, using, at least in parts, the same neurobiological components like other SM tools. Positive activities and cognitive behaviors ('thoughts') as well as moderate physical exercises neurobiologically project on the hypothalamus and the pituitary gland, i.e., the central stress axes, via prefrontal/frontolimbic pathways, thereby inducing a central vegetative stress reduction, making it possible to mentally (i.e., self-regulatory, deliberately) influence stress and autonomous functions throughout the body, e.g., mind-body medicine. Stress hormones, including NE, cortisol and CRH, get reduced, or their effects antagonized on the receptor level, while DA, opioids and opiates are endogenously enhanced, that is, their signalling systems initiated. Serotonin and DA improve physical endurance capacities and stress hardiness, as do the endorphins, subsequently, with endogenous MO presumably playing a role in the recovery phase of stress and/or strenuous exercise. The latter substances also improve mood and pain resistance, two critical features of a successful stress autoregulation. All these effects are potentially plastic, that is, learnable and modifiable.

Relaxation

We explicitly reported on the neurobiology of relaxation, i.e., the relaxation response (RR), a state of physiological hypoarousal opposite to the stress response, elsewhere, particularly with regard to a DA and MO involvement, coupled to NO signalling (e.g., see [Dusek et al. 2006; Esch & Stefano, 2007b; Esch et al. 2003b; Esch et al. 2004a; Esch et al. 2004b; Mantione et al. 2007; Mantione et al. 2008; Salamon et al. 2006; Stefano & Esch, 2005b; Stefano et al. 2001a; Stefano et al. 2005a; Stefano et al. 2006, Stefano et al. 2007]). However, the critical facts for our hypothesis of an overlapping neurobiological principle for SM processes and autoregulation, including relaxation, are these: constitutive NO signalling is critical in relaxation [Esch et al. 2002c; Salamon et al. 2006; Stefano & Esch, 2005b; Stefano et al. 2000d; Stefano et al. 2005a; Stefano et al. 2006]. When the enzyme constitutive NO synthase (cNOS) is stimulated, e.g., by relaxation induction, NO release occurs for a short period of time, but this level of NO can exert profound physiological actions for a longer period of time [de la Torre & Stefano, 2000; Stefano et al. 2000c; Stefano et al. 2000d]. NO is not only an immune, vascular and neural signalling molecule, it is also antibacterial, antiviral, scavenges free radicals, and it down-regulates endothelial and immunocyte activation and adherence, thus performing vital physiological activities, including vasodilation, i.e., blood pressure reduction [Benz, 2002a; Benz, 2002b; Esch et al. 2002c; Esch et al. 2003a; Esch et al. 2003b; Stefano, 1999; Stefano et al. 2000d; Stefano et al. 2006]. Hence, NO plays the role of an effector of autoregulation. Novel opiate selective mu opiate receptor subtypes, namely Mu3 (and Mu4), stimulate cNOS-derived NO release by MO, thus resulting in the down-regulation of immune, vascular, gut and neural tissues [Bilfinger & Stefano, 2000; Liu et al. 1996; Magazine et al. 1996; Mantione et al. 2008; Kream & Stefano, 2009b; Stefano & Kream, 2009c; Stefano et al. 2000a; Stefano et al. 2004; Stefano et al. 1995b; Stefano et al. 2009b].

Individuals who are relaxing experience peripheral vasodilation, warming of the skin, a decrease in heart rate and an overwhelming sense of well-being only when this can occur in a safe and trusted environment. Counter-intuitively, there may be initial sympathetic activation in relaxation, i.e., anticipatory stress response [Stefano et al. 2008c], as noted by NE levels, which initially go up [Hoffman et al. 1982]. This further appears to be the case for falling in love and enjoying similar, pleasurable experiences, since this does, for example, represent the risk of rejection [Dusek et al. 2008b; Esch & Stefano, 2004c; Marazziti & Cassano, 2003; Marazziti & Canale, 2004]. Also, it seems appropriate to 'screen' the environment by enhanced vigilance and alertness before relaxing, making it safe to slow-down and focus inwards, introversively. With reference to the vasodilator peripheral heat-warming processes, we surmise that this involves NO [Stefano et al. 2001a]. In regard to the sense of well-being, we can assume that this process may also involve opioid and opiate receptor activation by corresponding signalling molecules [Esch & Stefano, 2004c].

NO has the ability to block a sympathetic response simply by having its release occur beyond the basal level, which will lead to vasodilation and peripheral sense of warmth. Moreover, NO blocks NE effects on the receptor level [Esch et al. 2006b; Stefano et al. 2001a; Stefano et al. 2003]. Its presence can also explain the paradox of the presence of NE in plasma while vasodilation is taking place [Hoffman et al. 1982]. Recently, we demonstrated that during the RR NO levels are increased [Dusek et al. 2006; Mantione et al. 2007], i.e., NO release, further supporting the critical role of NO in this process. Additionally, endogenous MO signalling appears to play a role in relaxation: Many immune processes perpetuate and become embellished with time by the recruitment of cells, and through beneficial yet sometimes harmful signalling molecules such as the proinflammatory cytokines [Esch & Stefano, 2002e; Esch et al. 2002a; Esch et al. 2002c; Esch et al. 2003a; Stefano & Esch, 2005b]. These molecules can all be down-regulated by MO, which is released following stress or trauma [Stefano et al. 1996b; Stefano et al. 2000d], i.e., autoregulation, specifically via cNOS-derived NO under certain circumstances. Thus, MO may help overcome over-stimulated immune, vascular and neural tissues [Stefano et al. 2000d; Stefano et al. 2005d; Zhu et al. 2005a], particularly in stress, as well as maintain a basal level of microenvironmental inhibition, preventing inappropriate excitation from emerging [Stefano et al. 2000c]. Prior to NO release, this process also invokes the release of NE and opioid peptides.

Relaxation can be cognitively learned, that is, active induction of the RR [Baron Short et al. 2007; Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d; Stefano et al. 2005a]. This potential is always endogenously (constitutively) present, and only

after removing the sympathetic or stress reactions (disinhibition [Stefano et al. 2000a]), does it emerge. It is probably a critical process that provides for mammalian stress resistance and longevity, i.e., it is antibiosenescent. The underlying physiology is, to some extent, similar to the placebo response since this too involves the brain's neurobiological reward and motivation circuitries and the very same molecular effectors [Baron Short et al. 2007; de la Fuente-Fernández et al. 2001; de la Fuente-Fernández et al. 2006; Fricchione & Stefano, 2005; Fulda & Wetter, 2008; Sher, 2003; Stefano et al. 2001a; Stefano et al. 2007a]. Relaxation-associated NO possibly indicates a coupling to endogenous DA and MO release, since MO, at least in parts, originates from DA through enzymatic processing as noted earlier [Dusek *et al.* 2006; Kream & Stefano, 2009b; Mantione *et al.* 2007; Stefano & Kream, 2009c; Stefano *et al.* 2001a; Stefano *et al.* 2005d; Stefano *et al.* 2007a; Zhu *et al.* 2005b]. Furthermore, relaxation or meditation practices are capable of slowing-down and decrease the overall brain metabolism, while specific regional parts, e.g., necessary for autonomous control, attention and concentration, get activated [Khalsa *et al.* 2009; Lazar *et al.* 2000; Newberg *et al.* 2001]. For example, regular meditation potentially enhances mood and affect by inducing a left-anterior lateralization of brain activity [Davidson *et al.* 2003]. Thus, relaxation, meditation and other spiritual practices that incorporate some sort of relaxation exercise seem to make the brain work more effectively, in parts, by improving neurobiological plasticity, functional resilience and flexibility, which also includes stress resistance [Davidson *et al.* 2003; Esch *et al.* 2004a; Esch *et al.* 2004b; Lazar *et al.* 2005]. This ability may also represent a critical evolutionary advantage [Esch, 1999; Esch, 2003d; Rossano, 2007]. Central to our hypothesis is the significance of NE, NO, DA and MO signalling in stress and stress autoregulation, including relaxation, both in the central and peripheral nervous system. We find that NO and MO control catecholamine processes on many levels, including synthesis, release and actions. NO appears to be the physiological converging point of these said actions [Kream *et al.* 2007; Kream *et al.* 2009a; Mantione *et al.* 2008; Stefano & Kream, 2009c; Stefano & Kream, 2007b].

Nutrition

Food intake is an essential human activity and can truly be a source of pleasant feelings or sensations, and stress-reducing, at times, 'unfortunately' [Esch & Stefano, 2004c; Esch et al. 2006a]. This vital biological process is regulated by homeostatic and hedonic systems in the brain, i.e., limbic reward and motivation circuitries [Stefano & Esch, 2005b; Esch et al. 2004b; Esch et al. 2006a; Kringelbach, 2004]. Positive or appetitive motivation is mediated by neurochemical systems, e.g., within the nucleus accumbens. Hence, gamma-aminobutyric acid (GABAergic) neurons localized in the accumbens shell directly influence hypothalamic effector mechanisms for feeding motor patterns, yet they don't participate in the execution of more complex food seeking strategies and behaviors [Kelley et al. 2005]. Opioidergic neurons, i.e., opioid receptor positive (agonistic) neurons, distributed throughout the nucleus accumbens and caudate-putamen mediate the hedonic impact of palatable foods (high sugar, high fat), and these neurons are under modulatory control of striatal cholinergic interneurons [Esch et al. 2006a; Kelley et al. 2005]. Opiate alkaloids (e.g., MO) and opioid peptides (e.g., enkephalin) seem to differ in their ability to act on nucleus accumbens autoregulation related to palatability and taste [Esch et al. 2006a]. In particular, mu opioid receptors in the medial shell of the nucleus accumbens appear to critically regulate the hedonic impact, i.e., 'liking', of sweetness, food and drug rewards [Esch & Stefano, 2004c; Esch et al. 2004b; Pecina & Berridge, 2005]. Thus, with regard to the nucleus accumbens, there appears to be a specific locus responsible for opioidergic amplification of hedonic impact related to eating/tasting. However, recent experiments reveal a distinction between opioid mechanisms for actual food intake and its hedonic impact [Pecina & Berridge, 2005].

Pleasurable experiences like eating exert calming effects via release of GABA in the amygdala and other limbic areas: 'plenus venter non studet libenter' – a full stomach doesn't like to study, or get stressed [Campbell, 1999; Esch et al. 2004a; Esch et al. 2006a]. Thus, on the neurobiological level, pleasure involves autoregulatory substances that possess calming and anxiolytic capacities, including GABA or oxytocin, thereby facilitating feelings of well-being and relaxation [Esch & Stefano, 2004c; Esch & Stefano, 2005b; Esch & Stefano, 2005a; Esch et al. 2004a; Esch et al. 2004b; Stefano & Esch, 2005c; Stefano et al. 2008c]. Endogenous MO, as illustrated, acts as a central and peripheral down-regulator, primary or secondary (i.e., back-up), and its involvement in the neurobiological down-regulation associated with food and eating behaviors can be assumed [Esch et al. 2006a]. Even more, MO may play a direct and specific role in the pleasure-related signalling associated with eating. MO thereby seems to enhance feeding (i.e., hunger and subsequent food intake) by increasing the hedonic palatability and pleasantness of food, e.g., taste [Doyle et al. 1993; Esch et al. 2006a; Pecina & Berridge, 1995]. Yet, enhancement of food palatability may represent a critical psychological pathway by which opioid agonists generally induce feeding, i.e., food intake. In fact, such agonists, for example those selective for the Mu3 and 4 receptors (i.e., opiate alkaloids/endogenous MO [Esch et al. 2006a; Kelley et al. 2002]), induce a potent increase in food, sucrose, saccharin, salt, and ethanol intake [Kelley et al. 2002]. This general self-regulatory brain mechanism was beneficial during evolution for it ensured the consumption of relatively scarce high-energy food sources [Esch et al. 2006a; Kelley et al. 2002]. Besides MO being found in limbic tissues and the ventral tegmental area (VTA) of the brain, it has been localized and coupled to DA signalling in recent times as a MO precursor [Mantione et al. 2008; Stefano et al. 2007a; Stefano et al. 2008b; Zhu et al. 2005a; Zhu et al. 2005b]. Given the close connection between endogenous DA and MO biosynthesis, a reward-dependent behavioral motivation to eat (i.e., appetite) and the actual food-intake are closely related to DA-MO autoregulation

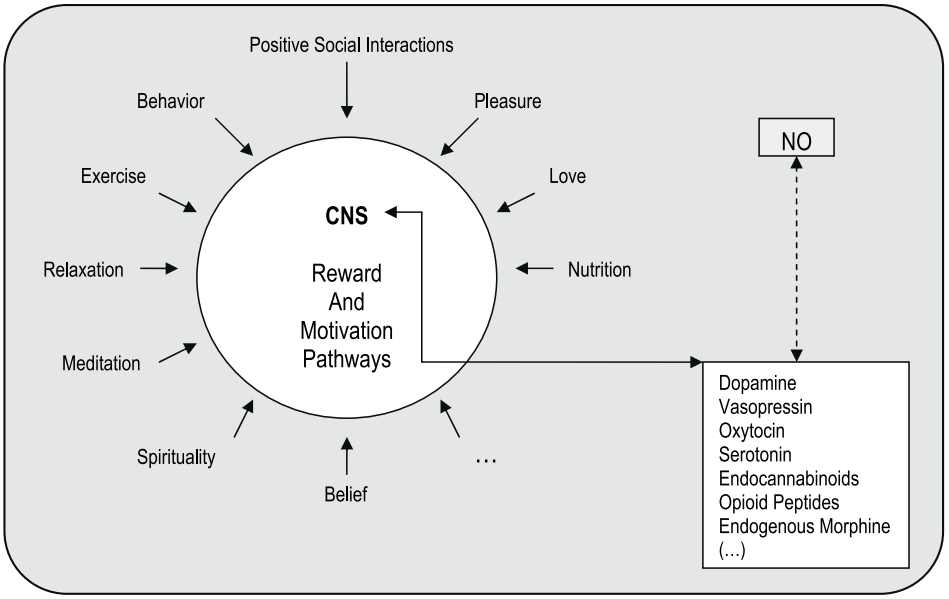

Figure 7: The common neurobiology of different stress management approaches and healing practices. Different stress-reducing techniques and practices act via autoregulatory central nervous system (CNS) reward and motivation circuitries, i.e., they share some parts of their physiology. We surmise that this commonality represents an overlapping and general (neuro-) biological principle of autoregulation, that is, a self-healing potential. Imbedded in these systems are various underlying signalling pathways and effector molecules with which the stress management techniques exert their beneficial results. Many of these signalling mechanisms converge on nitric oxide (NO) as their central and common effector, i.e., second or third messenger. Thus, NO is critically coupled to the reward physiology and stress self-regulation, and it can be found and experimentally measured in these very techniques; references: [Berridge & Kringelbach, 2008; Esch, 2008a; Esch & Stefano, 2004c; Esch & Stefano, 2005b; Esch & Stefano, 2007b; Esch et al. 2004a; Esch et al. 2004b; Esch et al. 2006b; Fricchione & Stefano, 2005; Kream & Stefano, 2009b; Stefano & Esch, 2005b; Stefano et al. 2003; Stefano et al. 2006; Stefano et al. 2007a].

[Esch & Stefano, 2004c; Esch et al. 2006a; Stefano et al. 2007a]. As noted earlier, MO via NO release can down-regulate energy metabolism at the mitochondrial level, complementing its actions on food intake [Kream & Stefano, 2009b].

Obese individuals seem to suffer a serotonergic and dopaminergic deficit, e.g., in the midbrain or hypothalamus (e.g., [Tomasi et al. 2009]), and they additionally show lower activation of the amygdala as a signal of a full stomach, that is, an impaired control of food intake (reduced aversion against further ingestion), during eating [Tomasi et al. 2009]. Thus, they eat more and don't feel full or receive the pleasure from it. On the other hand, hedonic taste reactions are enhanced in MO-treated – more 'hungry' – animals [Esch et al. 2006a]. Aversive food reactions remained unchanged, pointing towards a specific pleasure-relatedness of MO signalling in association with eating. Taken together, MO seems to enhance feeding by increasing the pleasantness of food, which in return reduces stress (see below).

The hedonic capacity of food is responsive to stress. Innate neurobiological feedback mechanisms may, this time, lead to a 'psychological trap', besides the immediate stress relief or 'ease' coming with eating: Stress, and chronic stress in particular, leads to elevated glucocorticoid levels in the blood, e.g., cortisol increase, since these molecules are part of the stress physiology (stress hormones) [Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d]. Corticoids exert their functions throughout the body, including the central nervous system (CNS), while easily passing the blood-brain-barrier. Together with insulin, glucocorticoids stimulate a drive for and ingestion of comfort foods, food that may directly result in a reduction of CNS stress effects, e.g., in the nucleus accumbens, through stimulation of the anterior, more pleasure-related and -stimulated part of this cell group, thus reducing the impact of the pain- or stress-stimulated, more defensive posterior part: by involving the pleasure potential of food, eating can be a neurobiological and vital source of stress reduction [Dallmann et al. 2005; Esch & Stefano, 2004c; Esch et al. 2006a]. However, the shift in caloric intake from simple maintenance foods to a preference for 'pleasure-inducing' comfort foods (high caloric, high fat and/or sugar, low fibre: 'fast food') during chronic stress, e.g., to better cope (i.e., fight or flight) and then endogenously reduce the initial stress, together with elevated stress hormones and insulin during these stress processes, may lead to an overall elevated energy uptake and reorganization of energy stores from a peripheral to a more central distribution, primarily as abdominal fat, which consequently imposes a health threat itself, i.e., as a result of chronic stress and the autoregulatory SM attempts: what is good in the short run can become deleterious in the long, or – 'too much is too much' [Dallmann et al. 2005; Esch et al. 2006a]. This caloric shift appears to reduce the influence of the chronic stress network on behaviors, autonomic and neuroendocrine outflow [Dallmann et al. 2005], yet advantageous food capacities to reduce stress may over time be

far outweighed by the consequences of a presumably unhealthy fat distribution and elevated blood fat levels, e.g., in chronic stress [Esch et al. 2002b; Esch et al. 2006a; Stefano et al. 2005a]. However, dieting as a strategy to reduce body weight often fails as it causes food cravings, leading to "bingeing" and weight regain, possibly not only involving DA but also opiate/opioid regulation [Esch et al. 2006a]. Also, stress resistance and mood may be lowered by chronic fasting [Esch et al. 2006a].

Taking in and 'digesting' negative information can also interfere with appetite and taste. In other words, the hedonic capacity of food is responsive to acute stress and depressive mood swings [Willner & Healy, 1994]. When our mood is low, we seek pleasure, i.e., reward, self-therapy, as long as biological flexibility, autoregulation and drive still exist [Esch, 2003d; Esch & Stefano, 2004c; Esch et al. 2004b]. The subsequent neurotransmitter boost, possibly involving serotonin, DA and opioid agonist or MO signalling, may stimulate or involve food intake as a 'supplement' for low mood swings and thereby, instead of solving the problem, possibly kicking off a vicious circle [Esch & Stefano, 2004c; Esch et al. 2006a]. Yes, eating may buffer against stress, but eating more as a consequence of chronic stress or depressive episodes may facilitate overweight which could then increase frustration or diminish positive and more effective coping strategies and behavioral problem solving, i.e., appetitive motivation and health promotion [Esch, 2003d; Esch, 2008a; Esch & Stefano, 2004c; Esch et al. 2006a; Esch et al. 2006b].

Taken together, food intake is an essential biological activity. Because it is so important, nature has linked eating to appetitive behavioral motivation, enhanced motor activity and its underlying neurobiology, including pleasure and reward processes [Stefano & Kream, 2007b]. These autoregulatory pathways are located within the brain, e.g., limbic system, orbitofrontal/frontobasal structures, nucleus accumbens, VTA etc., and they promote feelings of wellness and pleasure [Esch & Stefano, 2004c; Esch et al. 2006a]. In this way, the process of eating itself can be healthy, e.g., stress reduction via pleasure induction. Not only what we eat matters, but particularly how we actually realize it. Palatability, taste, and pleasantness of food as well as the mindful act of smelling, feeling, tasting are of major importance, and some of these functions are critically self-regulated [Ernst et al. 2009; Esch et al. 2006a]. Thus, all that we like about eating is part of this important and general hedonic motivational coupled motor system. Pleasure and eating use the same neurobiological pathways as other hedonic activities, e.g., love, positive psychology, relaxation, exercise etc. (***Fig. 7***), and all these experiences have the capacity to bring us joy, health and wellness, particularly through physiological stress reduction, thereby involving the very same effector systems, such as DA, MO, and the coupled NO signalling.

Discussion

Stress is natural and can be helpful. Stress at appropriate levels, for example, can improve problem solving and cognitive function [Huether et al. 1999; Stefano et al. 2005a; van Praag et al. 2008]. It may act as a trigger for adaptive modifications, e.g., of the structure and the function of the brain, and thus serve to adjust, in a self-optimizing and autoregulative manner, the behavior of an individual to the ever-changing requirements of its external world and environments [Esch, 2003d; Huether et al. 1999; Huether, 1996; McEwen, 2009]. In this regard, stress offers organisms a positive coping strategy, enabling the organism, so endowed, a greater chance of survival. In part, this explains why many of the stress components found at the cellular, tissue and organismic levels in protists, invertebrates and vertebrates have been preserved during the long course of evolution.

Stress can, however, have deleterious effects in all organisms, and these are related to the dose, form and duration of stress and its underlying (patho-) physiology [Esch et al. 2002a; Esch et al. 2002b; Esch et al. 2002d; Huether et al. 1999; Sachsse et al. 2002; Stefano et al. 2005a]. Accordingly, stress reduction/termination is an innate protection potential to ameliorate stress and counteract its dangerous downside. Hence, SM is natural too, but it has to be physiologically 'permitted'. The underlying autoregulation involved in stress and SM manifestations shows a neurobiological overlap (while not denying the specific parts and shares of SM approaches) pointing towards a more general neurobiological/life-sustaining principle, i.e., unspecific or common effects [Esch et al. 2004b; McEwen, 2001; McEwen, 2009]. In this, endogenous SM response pathways consist of the same 'hardware' and chemical messengers as, for example, the placebo response, namely the CNS motivation, motor and reward pathways, located predominantly in the limbic brain [Esch & Stefano, 2004c; McEwen, 2001; McEwen, 2009; Stefano et al. 2001a].

The basic truth appears to be that natural or biological and positive activities, i.e., comforting or 'wellness' interventions in cognitive and higher noncognitive organisms, serve the goal of survival, appetitive motivation and health for the individual and the species. These so endowed organisms are rewarded by an overlapping pleasure physiology (***Fig. 7***). The active use of such self-regulatory potentials may be principally possible, learnable and trainable, e.g., individually by the use of mind/body or cognitive behavioral SM techniques [Esch, 2008a; Esch & Stefano, 2007b; Komaroff, 2001], yet these activities and 'complementary medical' interventions (e.g., [Ernst et al. 2008; Ernst et al. 2009; Esch et al. 2004b; Esch et al. 2007a; Stefano & Esch, 2005b]) via their physiological effects are unconsciously and automatically self-activated during stress to reduce it. When used intentionally, we surmise, these activities may buffer against stress or prevent negative side effects of it, i.e., chronic stress [Esch, 2002f; Esch, 2003d; Esch, 2008a; Esch & Stefano, 2007b]. We further speculate that, based on this

knowledge, a novel medical strategy for health, including longevity, is at hand.

Nature, as it seems, selected only a handful of molecular key 'messenger' players, many converging on constitutive NO as their crucial messenger, to translate the stress-reducing potential into the mind and the body phenomenon [Esch & Stefano, 2007b; Esch et al. 2002c; Esch et al. 2003a; Stefano & Esch, 2005b]. In part, the building blocks of these common messengers may be based on their high level of availability in early life/evolution, i.e., tyrosine, arginine [Stefano & Kream, 2007b; Stefano & Kream, 2009c]. Hence, endogenous MO might serve as a central signalling molecule to realize the necessary down-regulation following stressful activities and encounters as well as maintain cell processes in a state of down regulation whereby they discriminate against excitatory 'noise'. This hypothesis is supported by the fact that plants make DA but do not use it as a signal molecule [Stefano & Kream, 2007b].

Professional SM training, as well as the endogenously activated intrinsic mechanisms to self-reduce stress (that possibly can be amplified or conditioned by SM training), use a broad array of different ways and tools to act on the neurobiological effector systems and pathways. Although subsequently converging, physiologically, the approaches come/start from different sides: SM acts via strong and broad biological pathways ('highways'), consisting, for example, of positive behaviors, exercise, relaxation, or nutrition (BERN – see ***Fig. 1***), including social support and spirituality. Because the limbic system is the critical region in the brain for the neurobiological realization of the SM potential, memory processes (e.g., hippocampus) and anxiety reduction (e.g., amygdala) are coupled to the SM physiology, making the individual overcome rational hesitance or cognitive dwelling ('cognitive constipation' [Stefano et al. 2005a]) in stress and SM, instead accessing and then memorizing a successful stress reduction strategy. Here, emotion may represent the short cut to action whereas too much cognitive dwelling may lead to inactivity [Stefano & Fricchione, 1995a]. In addition, behavior is constantly evaluated in the brain and rewarded by motivational circuitries, when regarded beneficial, thus inducing psycho-behavioral growth and development. Interestingly, growing older, maturing and going through stressful experiences as well as incidental stress hormone activity enhance DA levels also in the amygdala, thereby facilitating the acknowledgement of the self (self-perception) and self-regulation, since aversions against what might not be useful and self-supportive are thus enhanced, at least in rodents [Barr et al. 2009]. The amygdala, equally, is a critical region for the stress responses in humans, with a hyperactive amygdala indicating stress conditions. However, SM interventions decrease anxiety and perceived stress, which correlates positively with decreases in right basolateral amygdala grey matter density [Hölzel et al. 2009]. This too may represent an important biological reason why stress and the successful solving of an (intended, adventure-filled) stressful situation by SM activities, e.g., running, bungee jumping, stage performing, sex etc. [Esch & Stefano, 2004c; Esch & Stefano, 2005b; Salamon et al. 2005; Stefano et al. 2008c], can be highly pleasurable, rewarding, self-efficacious and finally relaxing (***Fig. 6***).

Beneficial behaviors and strategies to overcome stress are endogenously rewarded, that is, positively and physiologically amplified or reinforced, i.e., trained ('do it again'), and this happens via DA, endorphin, and MO release, apart from other messenger molecules. Thus, to gain the benefits of stress for development, flexibility, growth, health and survival [Esch, 2002f; Esch, 2003d; Stefano et al. 2005a], a non-linear and dynamic SM physiology has to be in place and functioning [Esch, 2003d; Esch & Stefano, 2007b; Esch et al. 2003b; Stefano & Esch, 2005b], so that, in the end, a full stress recovery is possible. For this, a physiological self-regulation capacity is necessary and has to be biologically possible. At the core of it, as we surmise, lies the DA-MO-NO autoregulation of SM.

Taken together, autoregulatory signalling messengers have the potential to act as physiological stress down-regulators, and they exert these effects possibly via pleasure-related brain pathways. Neurobiologically, these pathways represent a general or superordinated principle to terminate activated stress responses, since the stress physiology, though useful at times, has to be controlled and stopped in time. Following a stressful encounter and stress induction, that is, a physiological stress response initiation, endogenous SM potentials get activated to subsequently regulate and finally terminate initial stress, for example, via endogenous relaxation induction [Esch & Stefano, 2007b; Salamon et al. 2006; Stefano et al. 2006]. If the situation, however, calls for endurance and prolongation of stress mechanisms, e.g., because the original stressor or invader is not defeated, endorphins exemplarily [Stefano et al. 2005d] may serve as means to down-regulate or decrease the pain or exhaustion that comes with high or ongoing stress, i.e., fight or flight, while still up-regulating, for example, the immune system (e.g., proinflammation). Once the stressful situation is over, a general down-regulatory mechanism, including antiinflammation, as well as a secondary back-up/recovery system has to become activated, and this, as we surmise, is a key function of endogenous MO, which also leads to a psychological calming, i.e., relaxation and regeneration (psychological and physiological stress recovery – see above). Moreover, opiate as well as DA, oxytocin and endocannabinoid signalling have now been demonstrated in different health-promoting and self-regulatory techniques, including the placebo "therapy" [de la Fuente-Fernández et al. 2001; de la Fuente-Fernández et al. 2006; Esch & Stefano, 2004c; Esch & Stefano, 2005b; Esch et al. 2004b; Esch et al. 2006b; Fricchione & Stefano, 2005; Fulda & Wetter, 2008; Sher, 2003], which partially works, as we speculate, via the same DA-MO-NO cascade and therefore will be predominantly down-regulatory by its nature.

Conclusions

There is no doubt that different SM techniques, as they are explored, have different or specific physiological effects and components and possess unique medical properties. Exercise, for example, exerts its positive effects, e.g., on the cardiovascular, immune and neural systems, via different initial pathways than meditation or positive communication. However, there seems to exist a common neurobiological mechanism, i.e., limbic autoregulation, that involves DA, MO and other endogenous signalling systems, many of which act through NO release, and this appears to be of critical importance for the endogenous self-regulatory system and ability to manage stress as a useful and potentially health-promoting phenomenon. Hence, SM techniques at first glance are distinct and different from each other and then they finally reveal a joint neurobiology that is profound and effective, which developed through animals' evolution. We hypothesize that this common mechanism has a neurobiological root, which is highly significant since it was conserved through evolution.

SM builds on an innate self-healing process essential as an antibiosenescent phenomenon for health promotion and stress reduction, which offers medical therapeutic treatment options. Constitutive NO serves as an effector and converging point for this futuristic clinical treatment modality. Equally significant are the target messengers, DA and MO, as invoking novel counter-intuitive cNOS-derived NO release. These proposed medical interventions will reduce chronic stress-induced disorders. This novel approach in physiological stress reduction will also impact biomedical disorders associated with proinflammatory events.

As stress is natural so is SM (almost like day and night). However, we must take care to keep this healing potential in mind and reserve time and space in our daily routines and stressful lives to let autoregulation happen and, therefore, function. Otherwise we delay the ever accumulating 'stress' to deal with the mental and bodily consequences of a lowered stress-induced resistance to diseases. Importantly, stress reduction can be learned, it is neurobiologically rewarding and pleasurable and one must simply learn to take the first step.

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REFERENCES

1 Adler T. A complex relationship: Psychosocial stress, pollution, and health. Environ Health Perspect 2009; **117**: A407.
2 Astin JA, Shapiro SL, Eisenberg DM, Forys KL. Mind-body medicine: State of the science, implications for practice. J Am Board Fam Pract 2003; **16**: 131-147.
3 Atmanene C, Laux A, Glattard E, Muller A, Schoentgen F, Metz-Boutigue MH, Aunis D, Van Dorsselaer A, Stefano GB, Sanglier-Cianférani S, Goumon Y. Characterization of human and bovine phosphatidylethanolamine-binding protein (PEBP/RKIP) interactions with morphine and morphine-glucuronides determined by noncovalent mass spectrometry. Med Sci Monit 2009; **15**: BR178-87.
4 Bakoula C, Kolaitis G, Veltsista A, Gika A, Chrousos GP. Parental stress affects the emotions and behaviour of children up to adolescence: A Greek prospective, longitudinal study. Stress 2009; in press.
5 Baron Short E, Kose S, Mu Q, Borckardt J, Newberg A, George MS, Kozel FA. Regional brain activation during meditation shows time and practice effects: An exploratory fMRI study. Evid Based Complement Alternat Med 2007 (Epub).
6 Barr GA, Moriceau S, Shionoya K, Muzny K, Gao P, Wang S, Sullivan RM. Transitions in infant learning are modulated by dopamine in the amygdala. Nat Neurosci 2009; **12**: 1367-1369.
7 Ben-Sefer E, Ben-Natan M, Ehrenfeld M. Childhood obesity: Current literature, policy and implications for practice. Int Nurs Rev 2009; **56**: 166-173.
8 Benson H, Casey A. Stress Management. Special Health Report. Harvard Health Publications, Harvard University, Boston, 2008.
9 Benz D, Cadet P, Mantione K *et al.* Tonal nitric oxide and health: A free radical and a scavenger of free radicals. Med Sci Monit 2002a; **8**: RA1–4.
10 Benz D, Cadet P, Mantione K *et al.* Tonal nitric oxide and health: Antibacterial and -viral actions and implications for HIV. Med Sci Monit 2002b; **8**: RA27–31.
11 Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: Reward in humans and animals. Psychopharmacology 2008; **199**: 457-480.
12 Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Brain Res Rev 1998; **28**: 306-369.
13 Berridge KC. Pleasures of the brain. Brain Cogn 2003; **52**: 106-128.
14 Bilfinger TV, Stefano GB: Human aortocoronary grafts and nitric oxide release: Relationship to pulsatile pressure. Ann Thorac Surg 2000; **69**: 480–485.
15 Bilfinger TV, Vosswinkel JA, Cadet P, Rialas CM, Magazine HI, Stefano GB. Direct assessment and diminished production of morphine stimulated NO by diabetic endothelium from saphenous vein. Acta Pharmacol Sin 2002; **23**: 97-102.
16 Blumenthal JA, Sherwood A, Babyak MA, Watkins LL, Waugh R, Georgdiades A, Bacon SL, Hayano J, Coleman RE, Hinderliter A. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: A randomized controlled trial. JAMA 2005; **293**: 1626-1634.
17 Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, Valet M, Berthele A, Tolle TR. The Runner's High: Opioidergic mechanisms in the human brain. Cereb Cortex 2008; **18**: 2523-2531.
18 Boettcher C, Fellermeier M, Boettcher C, Dräger B, Zenk MH. How human neuroblastoma cells make morphine. Proc Natl Acad Sci USA 2005; **102**: 8495-8500.
19 Breard M, Sari MA, Frapart Y, Boucher JL, Ducrocq C, Grillon C. The endogenous neurotransmitter, serotonin, modifies neuronal nitric oxide synthase activities. Free Radic Res 2007; **41**: 413-423.
20 Brotto LA, Gorzalka BB, LaMarre AK. Melatonin protects against the effects of chronic stress on sexual behaviour in male rats. Neuroreport 2001; **12**: 3465-3469.
21 Campbell A. The limbic system and emotion in relation to acupuncture. Acupunct Med 1999; **17**: 124-128.
22 Cannon W. The emergency function of the adrenal medulla in pain and the major emotions. Am J Physiol 1914, **33**: 356-372.
23 Cannon WB, Pereira JR. Increase of adrenal secretion in fever. Proc Natl Acad Sci USA 1924a; **10**: 247-248.
24 Cannon WB, Querido A. The role of adrenal secretion in the chem-

ical control of body temperature. Proc Natl Acad Sci USA 1924b; **10**: 245-246.
25 Cannon WB. A note on the effect of asphyxia and afferent stimulation on adrenal secretion. Science 1917; **45**: 463-464.
26 Chanrion B, Mannoury la Cour C, Bertaso F, Lerner-Natoli M, Freissmuth M, Millan MJ, Bockaert J, Marin P. Physical interaction between the serotonin transporter and neuronal nitric oxide synthase underlies reciprocal modulation of their activity. Proc Natl Acad Sci USA 2007; **104**: 8119-8124.
27 Charmandari E, Tsigos C, Chrousos G. Endocrinology of the stress response. Annu Rev Physiol 2005; **67**: 259-284.
28 Chin EH, Love OP, Verspoor JJ, Williams TD, Rowley K, Burness G. Juveniles exposed to embryonic corticosterone have enhanced flight performance. Proc Biol Sci 2009; **276**: 499-50.
29 Cordellini S, Vassilieff VS. Decreased endothelium-dependent vasoconstriction to noradrenaline in acute-stressed rats is potentiated by previous chronic stress: nitric oxide involvement. Gen Pharmacol 1998; **30**: 79-83.
30 Croft JB, Mokdad AH, Power AK, Greenlund KJ, Giles WH. Public health surveillance of serious psychological distress in the United States. Int J Public Health 2009; **54** (Suppl 1): 4-6.
31 Dallman MF, Pecoraro NC, la Fleur SE. Chronic stress and comfort foods: self-medication and abdominal obesity. Brain Behav Immun 2005; **19**: 275-280.
32 Daubenmier JJ, Weidner G, Sumner MD, Mendell N, Merritt-Worden T, Studley J, Ornish D. The contribution of changes in diet, exercise, and stress management to changes in coronary risk in women and men in the multisite cardiac lifestyle intervention program. Ann Behav Med 2007; **33**: 57-68.
33 Davidson RJ, Kabat-Zinn J, Schumacher J, Rosenkranz M, Muller D, Santorelli SF *et al.* Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med 2003; **65**: 564-570.
34 de la Fuente-Fernández R, Lidstone S, Stoessl AJ. Placebo effect and dopamine release. J Neural Transm Suppl 2006; **70**: 415-418.
35 de la Fuente-Fernández R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. Science 2001; **293**: 1164-1166.
36 de la Torre JC, Stefano GB. Evidence that Alzheimer's disease is a microvascular disorder: The role of constitutive nitric oxide. Brain Res Rev 2000; **34**: 119–36.
37 Doyle TG, Berridge KC, Gosnell BA. Morphine enhances hedonic taste palatability in rats. Pharmacol Biochem Behav 1993; **46**: 745-749.
38 Dusek JA, Benson H. Mind-body medicine: a model of the comparative clinical impact of the acute stress and relaxation responses. Minn Med 2009; **92**: 47-50.
39 Dusek JA, Chang BH, Zaki J, Lazar S, Deykin A, Stefano GB, Wohlhueter AL, Hibberd PL, Benson H. Association between oxygen consumption and nitric oxide production during the relaxation response. Med Sci Monit 2006; **12**: CR 1-10.
40 Dusek JA, Hibberd PL, Buczynski B, Chang BH, Dusek KC, Johnston JM, Wohlhueter AL, Benson H, Zusman RM. Stress management versus lifestyle modification on systolic hypertension and medication elimination: A randomized trial. J Altern Complement Med 2008a; **14**: 129-138.
41 Dusek JA, Otu HH, Wohlhueter AL, Bhasin M, Zerbini LF, Joseph MG, Benson H, Libermann TA. Genomic counter-stress changes induced by the relaxation response. PLoS ONE 2008b; **3**: e2576.
42 Erickson K, Kramer AF. Exercise effects on cognitive and neural plasticity in older adults. Br J Sports Med 2008; (in press).
43 Ernst S, Esch SM, Esch T. [The impact of mindfulness-based interventions on health care.] Forsch Komplementmed 2009; **16**: 296-303.
44 Ernst S, Welke J, Heintze C, Gabriel R, Zoellner A, Kiehne S, Schwantes U, Esch T. Effects of mindfulness-based stress reduction on quality of life in nursing home residents: A feasibility study. Forsch Komplementmed 2008; **15**: 74-81.
45 Esch T, Duckstein J, Welke J, Braun V. Mind/body techniques for physiological and psychological stress reduction: Stress management via Tai Chi training – a pilot study. Med Sci Monit 2007a; **13**: CR488-497.
46 Esch T, Esch SM, Stefano GB. Pain, stress and relaxation: Involvement of basic biological principles and healthy autoregulation. Eur J Integr Med 2009a; **1**: 237-238.
47 Esch T, Guarna M, Bianchi E, Stefano GB. Meditation and limbic processes. Biofeedback 2004a; **32**: 22-32.
48 Esch T, Guarna M, Bianchi E, Zhu W, Stefano GB. Commonalities in the central nervous system's involvement with complementary medical therapies: Limbic morphinergic processes. Med Sci Monit 2004b; **10**: MS6-MS17.
49 Esch T, Kim JW, Stefano GB. Neurobiological implications of eating healthy. Neuro Endocrinol Lett 2006a; **27**: 21-33.
50 Esch T, Michalsen A, Stefano GB. [Endocannabinoids as molecular instruments of health promotion]. Med Monatsschr Pharmazeut 2006b; **29**: 397-403.
51 Esch T, Stefano GB, Fricchione GL, Benson H. An overview of stress and its impact in immunological diseases. Mod Asp Immunobiol 2002a; **2**: 187-192.
52 Esch T, Stefano GB, Fricchione GL, Benson H. Stress in cardiovascular diseases. Med Sci Monit 2002b; **8**: RA93-RA101.
53 Esch T, Stefano GB, Fricchione GL, Benson H. Stress-related diseases: A potential role for nitric oxide. In: Stefano GB (ed.). Biomedical significance of nitric oxide. Medical Science International, New York, 2003a.
54 Esch T, Stefano GB, Fricchione GL, Benson H. Stress-related diseases: A potential role for nitric oxide. Med Sci Monit 2002c; 8: RA 103-118.
55 Esch T, Stefano GB, Fricchione GL, Benson H. The role of stress in neurodegenerative diseases and mental disorders. Neuroendocrinol Lett 2002d; **23**: 199-208.
56 Esch T, Stefano GB, Fricchione GL. The therapeutic use of the relaxation response in stress-related diseases. Med Sci Monit 2003b; **9**: RA23-34.
57 Esch T, Stefano GB. A bio-psycho-socio-molecular approach to pain and stress management. Forsch Komplementmed 2007b; **14**: 224-234.
58 Esch T, Stefano GB. Love promotes health. Neuroendocrinol Lett 2005a; **26**: 264-267.
59 Esch T, Stefano GB. Proinflammation: A common denominator or initiator of different pathophysiological disease processes. Med Sci Monit 2002e; **8**: HY1-9.
60 Esch T, Stefano GB. The neurobiology of love. Neuroendocrinol Lett 2005b; **26**: 175-192.
61 Esch T, Stefano GB. The neurobiology of pleasure, reward processes, addiction and their health implications. Neuroendocrinol Lett 2004c; **25**: 235-251.
62 Esch T. [Determination of processes for the active preservation of cellular autonomy and organisation by the use of the sister-chromatid exchange method]. Dissertation Thesis, Georg-August-Universitaet Goettingen, 1999.
63 Esch T. [Health in stress: Change in the stress concept and its significance for prevention, health and life style]. Gesundheitswesen 2002f; **64**: 73-81.
64 Esch T. [Healthy despite (and with!) music. The significance of music for motivation, reward and stress reduction.] Orchester 2009b; **57**: 18-19.
65 Esch T. [Music medicine: Music in association with harm and healing]. Musikphysiol Musikermed 2003c; **10**: 213-224.
66 Esch T. [Stress, adaptation, and self-organization: Balancing processes facilitate health and survival]. Forsch Komplementarmed Klass Naturheilkd 2003d; **10**: 330-341.
67 Esch T. Endocannabinoid signaling in stress, medicine and wellness. Med Sci Monit 2005c; **11**: ED3-5.
68 Esch T. Mind-Body-Medizin: Stress, Stressmanagement und Gesundheitsförderung. [Mind-Body Medicine: Stress, stress management and health promotion]. Kompl Integr Med 2008a; **49**: 35-39.
69 Esch T. Musical healing in mental disorders. In: Stefano GB, Bernstein S, Kim M (eds.). Musical healing. Medical Science International, New York, 2003e.
70 Esch T. Vom Verhalten zu den Molekülen: Ein biopsychosoziomolekularer Zugang zu Stress- und Schmerzlinderung. In: Niewöhner J, Beck S (eds.). Wie geht Kultur unter die Haut? Emergente Praxen an der Schnittstelle von Medizin, Lebens- und Sozialwissenschaft. Transcript Verlag, Bielfeld 2008b.
71 Foster PL. Stress responses and genetic variation in bacteria. Mutat Res 2005; **569**: 3-11.
72 Fricchione G, Stefano GB. Placebo neural systems: Nitric oxide, morphine and the dopamine brain reward and motivation circuitries. Med Sci Monit 2005; **11**: MS54-65.

73 Fricchione G, Zhu W, Cadet P, Mantione KJ, Bromfield E, Madsen J, DeGirolami U, Dworetzky B, Vaccaro B, Black P, Stefano GB. Identification of endogenous morphine and a mu3-like opiate alkaloid receptor in human brain tissue taken from a patient with intractable complex partial epilepsy. Med Sci Monit 2008;**14**: CS45-49.

74 Fricchione GL, Cytryn L, Bilfinger TV, Stefano GB. Cell behavior and signal molecule involvement in a case study of malignant histiocytosis: A negative model of morphine as an immunoregulator. Am J Hematol 1997; **56**: 197-205.

75 Fricchione GL, Stefano GB: The stress response and autoimmunoregulation. Adv Neuroimmunol 1994; **4**: 13–28.

76 Fulda S, Wetter TC. Where dopamine meets opioids: A meta-analysis of the placebo effect in restless legs syndrome treatment studies. Brain 2008; **131**: 902-917.

77 Galhardo RS, Hastings PJ, Rosenberg SM. Mutation as a stress response and the regulation of evolvability. Crit Rev Biochem Mol Biol 2007; **42**: 399-435.

78 Gertz K, Priller J, Kronenberg G, Fink KB, Winter B, Schröck H, Ji S, Milosevic M, Harms C, Böhm M, Dirnagl U, Laufs U, Endres M. Physical activity improves long-term stroke outcome via endothelial nitric oxide synthase-dependent augmentation of neovascularization and cerebral blood flow. Circ Res 2006; **99**: 1132-1140.

79 Giuliodori AM, Gualerzi CO, Soto S, Vila J, Tavio MM. Review on bacterial stress topics. Ann NY Acad Sci 2007; **1113**: 95-104.

80 Gold SM, Mohr DC, Huitinga I, Flachenecker P, Sternberg EM, Heesen C. The role of stress-response systems for the pathogenesis and progression of MS. Trends Immunol 2005; **26**: 644-652.

81 Gottholmseder G, Nowotny K, Pruckner GJ, Theurl E. Stress perception and commuting. Health Econ 2009; **18**: 559-576.

82 Gould E, McEwen BS, Tanapat P, Galea LAM, Fuchs E. Neurogenesis in the dentate gyrus of the adult tree shrew is regulated by psychosocial stress and NMDA receptor activation. J Neurosci 1997; **17**: 2492-2498.

83 Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. J Psychosom Res 2004; **57**: 35-43.

84 Guarna M, Ghelardini C, Galeotti N, Bartolini A, Noli L, Neri C, Stefano GB, Bianchi E. Effects of endogenous morphine deprivation on memory retention of passive avoidance learning in mice. Int J Neuropsychopharmacol 2004; **7**: 311-319.

85 Gumusel B, Orhan D, Tolunay O, Uma S. The role of nitric oxide in mediating nonadrenergic, noncholinergic relaxation in rat pulmonary artery. Nitric Oxide 2001; **5**: 296-301.

86 Herholz K, Buskies W, Rist M, Pawlik G, Hollmann W, Heiss WD. Regional cerebral blood flow in man at rest and during exercise. J Neurol 1987; **234**: 9-13.

87 Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: Exercise effects on brain and cognition. Nat Rev Neurosci 2008; **9**: 58-65.

88 Hoffman JW, Benson H, Arns PA et al: Reduced sympathetic nervous system responsivity associated with the relaxation response. Science 1982; **215**: 190–192.

89 Hollman W, Strueder HK. Exercise, physical activity, nutrition, and the brain. Nutr Rev 1996; **54**: 537-543.

90 Hollmann W, Strueder HK. Brain function, mind, mood, nutrition, and physical exercise. Nutrition 2000a; **16**: 516-5.

91 Hollmann W, Strueder HK. Brain, psyche and physical activity. Orthopade 2000b; **29**: 948-956.

92 Hölzel BK, Carmody J, Evans KC, Hoge EA, Dusek JA, Morgan L, Pitman RK, Lazar SW. Stress reduction correlates with structural changes in the amygdala. Soc Cogn Affect Neurosci 2009; (in press).

93 Howard GS. Adapting human lifestyles for the 21st century. Am Psychol 2000; **55**: 509-515.

94 Huether G, Doering S, Rüger U, Rüther E, Schüssler G. The stress-reaction process and the adaptive modification and reorganization of neuronal networks. Psychiatry Res 1999; **87**: 83-95.

95 Huether G. The central adaptation syndrome: Psychosocial stress as a trigger for adaptive modifications of brain structure and brain function. Prog Neurobiol 1996; **48**: 569-612.

96 Hughes TK Jr, Smith EM, Chin R, Cadet P, Sinisterra J, Leung MK, Shipp MA, Scharrer B, Stefano GB. Interaction of immunoactive monokines (interleukin 1 and tumor necrosis factor) in the bivalve mollusc Mytilus edulis. Proc Natl Acad Sci USA 1990; **87**: 4426-4429.

97 Jones F, Bright J, Clow A. Stress: Myth, Theory and Research. New York: Prentice Hall; 2001.

98 Kabat-Zinn J, Massion AO, Kristeller J, Peterson LG, Fletcher KE, Pbert L, Lenderking WR, Santorelli SF. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. Am J Psychiatry 1992; **149**: 936-943.

99 Kabat-Zinn J, Wheeler E, Light T, Skillings A, Scharf MJ, Cropley TG, Hosmer D, Bernhard JD. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). Psychosom Med 1998; **60**: 625-632.

100 Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Opioid modulation of taste hedonics within the ventral striatum. Physiol Behav 2002; **76**: 365-377.

101 Kelley AE, Baldo BA, Pratt WE, Will MJ. Corticostriatal-hypothalamic circuitry and food motivation: integration of energy, action and reward. Physiol Behav 2005; **86**: 773-795.

102 Khalsa DS, Amen D, Hanks C, Money N, Newberg A. Cerebral blood flow changes during chanting meditation. Nucl Med Commun 2009; **30**: 956-961.

103 Komaroff AL. Mind-Body Medicine: A Special Health Report. Boston: Harvard Health Publications, 2001.

104 Kream RM, Mantione KJ, Sheehan M, Stefano GB. Morphine's chemical messenger status in animals. Act Nerv Super Rediviva 2009a; **51**(1-2): 46–54.

105 Kream RM, Sheehan M, Cadet P, Mantione KJ, Zhu W, Casares FM, Stefano GB. Persistence of evolutionary memory: Primordial six-transmembrane helical domain mu opiate receptors selectively linked to endogenous morphine signaling. Med Sci Monit 2007; **13**: SC5-SC6.

106 Kream RM, Stefano GB. Endogenous morphine and nitric oxide coupled regulation of mitochondrial processes. Med Sci Monit 2009b; **15**: RA263-268.

107 Kringelbach ML. Food for thought: hedonic experience beyond homeostasis in the human brain. Neuroscience 2004; 126: 807-819.

108 Kringelbach ML. The human orbitofrontal cortex: Linking reward to hedonic experience. Nat Rev Neurosci 2005; **6**: 691-702.

109 Lazar SW, Bush G, Gollub RL, Fricchione GL, Khalsa G, Benson H. Functional brain mapping of the relaxation response and meditation. Neuroreport 2000; **11**: 1581-1585.

110 Lazar SW, Kerr CE, Wasserman RH, Gray JR, Greve DN, Treadway MT, McGarvey M, Quinn BT, Dusek JA, Benson H, Rauch SL, Moore CI, Fischl B. Meditation experience is associated with increased cortical thickness. Neuroreport 2005; **16**: 1893-1897.

111 Le Tourneau M. Mind-body medicine for stress management and opportunities at NCCAM. Altern Ther Health Med 2003; 9: 18.

112 Lee Duckworth A, Steen TA, Seligman ME. Positive psychology in clinical practice. Annu Rev Clin Psychol 2005; **1**: 629-651.

113 Liu Y, Shenouda D, Bilfinger TV, Stefano ML, Magazine HI, Stefano GB. Morphine stimulates nitric oxide release from invertebrate microglia. Brain Res 1996; **722**: 125–131.

114 Magazine HI, Liu Y, Bilfinger TV et al: Morphine-induced conformational changes in human monocytes,granulocytes, and endothelial cells and in invertebrate immunocytes and microglia are mediated by nitric oxide. J Immunol 1996; **156**: 4845–4850.

115 Mahler SV, Smith KS, Berridge KC. Endocannabinoid hedonic hot spot for sensory pleasure: Anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. Neuropsychopharmacology 2007; **32**: 2267-2278.

116 Mantione KJ, Cadet P, Zhu W, Kream RM, Sheehan M, Fricchione GL, Goumon Y, Esch T, Stefano GB. Endogenous morphine signaling via nitric oxide regulates the expression of CYP2D6 and COMT: Autocrine/paracrine feedback inhibition. Addict Biol 2008; **13**: 118-123.

117 Mantione KJ, Esch T, Stefano GB. Detection of nitric oxide in exhaled human breath: Exercise and resting determinations. Med Sci Monit 2007; **13**: MT1-5.

118 Mantione KJ, Goumon Y, Esch T, Stefano GB. Morphine 6beta glucuronide: Fortuitous morphine metabolite or preferred peripheral regulatory opiate? Med Sci Monit 2005; **11**: MS43-46.

119 Marazziti D, Canale D: Hormonal changes when falling in love. Psychoneuroendocrinology 2004; **29**: 931–936.

120 Marazziti D, Cassano GB: The neurobiology of attraction. J Endocrinol Invest 2003; **26**: 58–60.

121 McCarty R, Gold P. Catecholamines, Stress, and Disease: A Psychobiological Perspective. Psychosom Med 1996; **58**: 590-597.
122 McEwen BS. Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators. Eur J Pharmacol 2008; **583**: 174-185.
123 McEwen BS. Plasticity of the hippocampus: Adaptation to chronic stress and allostatic load. Ann NY Acad Sci 2001; **933**: 265-277.
124 McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med 1998; **338**: 171-179.
125 McEwen BS. The brain is the central organ of stress and adaptation. Neuroimage 2009; **47**: 911-913.
126 Metz U, Welke J, Esch T, Renneberg B, Braun V, Heintze C. Perception of Stress and Quality of life in overweight and obese people – Implications for preventive consultancies in primary care. Med Sci Monit 2009; **15**: PH1-6.
127 Meyer SE, Chrousos GP, Gold PW. Major depression and the stress system: A life span perspective. Dev Psychopathol 2001; **13**: 565-580.
128 Michalsen A, Grossman P, Acil A, Langhorst J, Luedtke R, Esch T, Stefano GB, Dobos GJ. Rapid stress reduction and anxiolysis among distressed women as a consequence of a three-month intensive yoga program. Med Sci Monit 2005; **11**: CR555-561.
129 Moles A, Kieffer BL, D'Amato FR. Deficit in attachment behavior in mice lacking the mu-opioid receptor gene. Science 2004; **304**: 1888-1889.
130 Negrao AB, Deuster PA, Gold PW, Singh A, Chrousos GP. Individual reactivity and physiology of the stress response. Biomed Pharmacother 2000; **54**: 122-128.
131 Neri C, Ghelardini C, Sotak B, Palmiter RD, Guarna M, Stefano GB, Bianchi E. Dopamine is necessary to endogenous morphine formation in mammalian brain in vivo. J Neurochem 2008; **106**: 2337-2344.
132 Newberg A, Alavi A, Baime M, Pourdehnad M, Santanna J, d'Aquili E. The measurement of regional cerebral blood flow during the complex cognitive task of meditation: A preliminary SPECT study. Psychiatry Res 2001; **106**: 113-122.
133 Olsen P, Rasmussen M, Zhu W, Tonnesen E, Stefano GB. Human gliomas contain morphine. Med Sci Monit 2005; **11**: MS18-21.
134 Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, Sparler S, Armstrong WT, Ports TA, Kirkeeide RL, Hogeboom C, Brand RJ. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998; **280**: 2001-2007.
135 Panksepp J. Neurologizing the psychology of affects: How appraisal-based constructivism and basic emotion theory can coexist. Persp Psychol Sci 2007; **2**: 281-296.
136 Pecina S, Berridge KC. Central enhancement of taste pleasure by intraventricular morphine. Neurobiology 1995; **3**: 269-280.
137 Pecina S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? J Neurosci 2005; **25**: 11777-11786.
138 Poeaknapo C, Schmidt J, Brandsch M, Dräger B, Zenk MH. Endogenous formation of morphine in human cells. Proc Natl Acad Sci USA 2004; **101**: 14091-14096.
139 Poeaknapo C. Mammalian morphine: de novo formation of morphine in human cells. Med Sci Monit 2005; **11**: MS6-17.
140 Pollak DD, Monje FJ, Zuckerman L, Denny CA, Drew MR, Kandel ER. An animal model of a behavioral intervention for depression. Neuron 2008; **60**: 149-161.
141 Richardson KM, Rothstein HR. Effects of occupational stress management intervention programs: A meta-analysis. J Occup Health Psychol 2008; **13**: 69-93.
142 Rojas Vega S, Strueder HK, Wahrmann BV, Bloch W, Hollmann W. Bicarbonate reduces serum prolactin increase induced by exercise to exhaustion. Med Sci Sports Exerc 2006a; **38**: 675-680.
143 Rojas Vega S, Strueder HK, Wahrmann BV, Schmidt A, Bloch W, Hollmann W. Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. Brain Res 2006b; **1121**: 59-65.
144 Rossano MJ. Did meditating make us human? Camb Archaeol J 2007; **17**: 47-58.
145 Roustit C, Chaix B, Chauvin P. Family breakup and adolescents' psychosocial maladjustment: Public health implications for family disruptions. Pediatrics 2007; **120**: e984-991.
146 Sachsse U, Von der Heyde S, Huether G. Stress regulation and self-mutilation. Am J Psychiatry 2002; **159**: 672.
147 Salamon E, Esch T, Stefano GB. Pain and relaxation. Int J Mol Med 2006; **18**: 465-470.
148 Salamon E, Esch T, Stefano GB. Role of amygdala in mediating sexual and emotional behavior via coupled nitric oxide release. Acta Pharmacol Sin 2005; **26**: 389-395.
149 Salavecz G, Chandola T, Pikhart H, Dragano N, Siegrist J, Jöckel KH, Erbel R, Pajak A, Malyutina S, Kubinova R, Marmot M, Bobak M, Kopp M. Work stress and health in Western European and post-communist countries: An East-West comparison study. J Epidemiol Community Health 2009; (in press).
150 Salzet M, Cocquerelle C, Verger-Bocquet M et al: Leech immunocytes contain proopiomelanocortin: nitric oxide mediates hemolymph POMC processing. J Immunol 1997a; **159**: 5400–11.
151 Salzet M, Stefano GB: Invertebrate proenkephalin: Delta opioid binding sites in leech ganglia and immunocytes. Brain Res 1997b; **768**: 224–32.
152 Salzet M, Stefano GB: Prodynorphin in invertebrates. Mol Brain Res 1997c; **52**: 46–52.
153 Sapolsky RM. Stress and plasticity in the limbic system. Neurochem Res 2003; **28**: 1735-1742.
154 Sapolsky RM. Why zebras don't get ulcers. Owl, USA, 2004.
155 Schulz U, Pischke CR, Weidner G, Daubenmier J, Elliot-Eller M, Scherwitz L, Bullinger M, Ornish D. Social support group attendance is related to blood pressure, health behaviours, and quality of life in the Multicenter Lifestyle Demonstration Project. Psychol Health Med 2008; **13**: 423-437.
156 Schwartz GE. Stress management in occupational settings. Public Health Rep 1980; **95**: 99-108.
157 Selye H. Implications of stress concept. N Y State J Med 1975; **75**: 2139-2145.
158 Selye H. The evolution of the stress concept. Am Sci 1973; **61**: 692-699.
159 Sher L. The placebo effect on mood and behavior: Possible role of opioid and dopamine modulation of the hypothalamic-pituitary-adrenal system. Forsch Komplementarmed Klass Naturheilkd 2003; **10**: 61-68.
160 Siegel RD (ed.). Positive Psychology. Special Health Report. Harvard Health Publications, Harvard University, Boston, 2009.
161 Siegrist J, Wahrendorf M. Quality of work, health, and retirement. Lancet 2009; (in press).
162 Sin NL, Lyubomirsky S. Enhancing well-being and alleviating depressive symptoms with positive psychology interventions: a practice-friendly meta-analysis. J Clin Psychol 2009; **65**: 467-487.
163 Smith KS, Berridge KC. Opioid limbic circuit for reward: Interaction between hedonic hotspots of nucleus accumbens and ventral pallidum. J Neurosci 2007; **27**: 1594-1605.
164 Stauder A, Konkoly Thege B, Kovacs ME, Balog P, Williams VP, Williams RB. Worldwide stress: Different problems, similar solutions? Cultural adaptation and evaluation of a standardized stress management program in Hungary. Int J Behav Med 2009 (in press).
165 Stefano GB, Benson H, Fricchione GL, Esch T (eds.). The Stress Response: Always Good and When It Is Bad. Medical Science International, New York 2005a.
166 Stefano GB, Bianchi E, Guarna M, Fricchione GL, Zhu W, Cadet P, Mantione KJ, Casares FM, Kream RM, Esch T. Nicotine, alcohol and cocaine coupling to reward processes via endogenous morphine signaling: The dopamine-morphine hypothesis. Med Sci Monit 2007a; **13**: RA91-102.
167 Stefano GB, Cadet P, Dokun A, Scharrer B. A neuroimmunoregulatory-like mechanism responding to stress in the marine bivalve Mytilus edulis. Brain Behav Immun 1990; **4**: 323-329.
168 Stefano GB, Cadet P, Zhu W et al: The blueprint for stress can be found in invertebrates. Neuroendocrinol Lett 2002; **23**: 85–93.
169 Stefano GB, Esch T, Cadet P, Zhu W, Mantione K, Benson H. Endocannabinoids as autoregulatory signaling molecules: Coupling to nitric oxide and a possible association with the relaxation response. Med Sci Monit 2003; **9**: RA 63-75.
170 Stefano GB, Esch T, Kream RM. Xenobiotic perturbation of endogenous morphine signaling: Paradoxical opiate hyperalgesia. Med Sci Monit 2009a; **15**: RA107-110.
171 Stefano GB, Esch T. Integrative medical therapy: Examination of meditation's therapeutic and global medicinal outcomes via nitric oxide. Int J Mol Med 2005b; **16**: 621-630.
172 Stefano GB, Esch T. Love and stress. Neuroendocrinol Lett 2005c; **26**: 173-174.

173 Stefano GB, Fricchione G, Goumon Y, Esch T. Pain, immunity, opiate and opioid compounds and health. Med Sci Monit 2005d; **11**: MS47-53.
174 Stefano GB, Fricchione GL, Esch T. Relaxation: Molecular and physiological significance. Med Sci Monit 2006; **12**: HY21-31.
175 Stefano GB, Fricchione GL, Slingsby BT, Benson H. The placebo effect and relaxation response: Neural processes and their coupling to constitutive nitric oxide. Brain Res: Brain Res Rev 2001a; **35**: 1-19.
176 Stefano GB, Fricchione GL. The biology of deception: Emotion and morphine. Med Hypotheses 1995a; **49**: 51-54.
177 Stefano GB, Goumon Y, Bilfinger TV et al: Basal nitric oxide limits immune, nervous and cardiovascular excitation: Human endothelia express a mu opiate receptor. Prog Neurobiol 2000a; **60**: 531–544.
178 Stefano GB, Goumon Y, Bilfinger TV et al: Basal nitric oxide limits immune, nervous and cardiovascular excitation: Human endothelia express a mu opiate receptor. Progress in Neurobiology 2000b; **60**: 513–30.
179 Stefano GB, Goumon Y, Bilfinger TV, Welters I, Cadet P. Basal nitric oxide limits immune, nervous and cardiovascular excitation: Human endothelia express a mu opiate receptor. Prog Neurobiol 2000c; **60**: 513-530.
180 Stefano GB, Goumon Y, Casares F et al: Endogenous morphine. Trends in Neurosciences 2000d; **9**: 436–42.
181 Stefano GB, Hartman A, Bilfinger TV et al: Presence of the mu3 opiate receptor in endothelial cells: Coupling to nitric oxide production and vasodilation. J Biol Chem 1995b; **270**: 30290–30293.
182 Stefano GB, Kream R. Endogenous opiates, opioids, and immune function: Evolutionary brokerage of defensive behaviors. Semin Cancer Biol 2008a; **18**: 190-198.
183 Stefano GB, Kream RM, Esch T. Revisiting tolerance from the endogenous morphine perspective. Med Sci Monit 2009b; **15**: RA189-198.
184 Stefano GB, Kream RM, Mantione KJ, Sheehan M, Cadet P, Zhu W, Bilfinger TV, Esch T. Endogenous morphine/nitric oxide-coupled regulation of cellular physiology and gene expression: Implications for cancer biology. Semin Cancer Biol 2008b; **18**: 199-210.
185 Stefano GB, Kream RM. Dopamine, Morphine, and Nitric Oxide: An Evolutionary Signaling Triad. CNS Neurosci Ther 2009c; in press.
186 Stefano GB, Kream RM. Endogenous morphine synthetic pathway preceded and gave rise to catecholamine synthesis in evolution (Review). Int J Mol Med 2007b; **20**: 837-841.
187 Stefano GB, Leung MK, Bilfinger TV, Scharrer B: Effect of prolonged exposure to morphine on responsiveness of human and invertebrate immunocytes to stimulatory molecules. J Neuroimmunol 1995c; **63**: 175–81.
188 Stefano GB, Murga J, Benson H, Zhu W, Bilfinger TV, Magazine HI. Nitric oxide inhibits norepinephrine stimulated contraction of human internal thoracic artery and rat aorta. Pharmacol Res 2001b; **43**: 199-203.
189 Stefano GB, Prevot V, Cadet P, Dardik I. Vascular pulsations stimulating nitric oxide release during cyclic exercise may benefit health: a molecular approach (review). Int J Mol Med 2001c; **7**: 119-129.
190 Stefano GB, Salzet B, Fricchione GL: Enkelytin and opioid peptide association in invertebrates and vertebrates: Immune activation and pain. Immunol Today 1998a; **19**: 265–68.
191 Stefano GB, Salzet-Raveillon B, Salzet M: Mytilus edulis hemocytes contains pro-opiomelanocortin: LPS and morphine stimulate differential processing. Mol Brain Res 1998b; **63**: 340–50.
192 Stefano GB, Salzet-Raveillon B, Salzet M: Mytilus edulis hemolymph contain prodynorphin. Immunol Lett 1998c; **63**: 33–39.
193 Stefano GB, Scharrer B, Bilfinger TV et al: A novel view of opiate tolerance. Adv Neuroimmunol 1996a; **6**: 265–77.
194 Stefano GB, Scharrer B, Smith EM et al: Opioid and opiate immunoregulatory processes. Crit Rev in Immunol 1996b; **16**: 109–44.
195 Stefano GB, Scharrer B: Endogenous morphine and related opiates, a new class of chemical messengers. Adv Neuroimmunol 1994; **4**: 57–68.
196 Stefano GB, Stefano JM, Esch T. Anticipatory Stress Response: A significant commonality in stress, relaxation, pleasure and love responses. Med Sci Monit 2008c; **14**: RA17-21.
197 Stefano GB, Zhu W, Cadet P, Mantione K: Morphine enhances nitric oxide release in the mammalian gastrointestinal tract via the mu3 opiate receptor subtype: A hormonal role for endogenous morphine. J Physiol Pharmacol 2004; **55**: 279–288.
198 Stefano GB. Endocannabinoid immune and vascular signaling. Acta Pharmacol Sin 2000e; **21**: 1071-1081.
199 Stefano GB: Substance abuse and HIV-gp120: Are opiates protective? Arch Immunol Therap Exp 1999; **47**: 99–106.
200 Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. In: Fisher S, Reason J, editors. Handbook of life stress, cognition and health. John Wiley and Sons, New York, 1988.
201 Stroth S, Hille K, Spitzer M, Reinhardt R. Aerobic endurance exercise benefits memory and affect in young adults. Neuropsychol Rehabil 2009; **19**: 223-243.
202 Stuckler D, Basu S. The International Monetary Fund's effects on global health: Before and after the 2008 financial crisis. Int J Health Serv 2009; **39**: 771-781.
203 Tomasi D, Wang GJ, Wang R, Backus W, Geliebter A, Telang F, Jayne MC, Wong C, Fowler JS, Volkow ND. Association of body mass and brain activation during gastric distention: Implications for obesity. PLoS One 2009; **4**: e6847.
204 Umathe SN, Bhutada PS, Jain NS, Mundhada YR, Borkar SS, Dhumal B. Role of nitric oxide in obsessive-compulsive behavior and its involvement in the anti-compulsive effect of paroxetine in mice. Nitric Oxide 2009; (in press).
205 van Donkelaar EL, van den Hove DL, Blokland A, Steinbusch HW, Prickaerts J. Stress-mediated decreases in brain-derived neurotrophic factor as potential confounding factor for acute tryptophan depletion-induced neurochemical effects. Eur Neuropsychopharmacol 2009; (in press).
206 van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 2005; **25**: 8680-8685.
207 van Praag H. Neurogenesis and exercise: Past and future directions. Neuromolecular Med 2008; **10**: 128-140.
208 van Wijk EP, Luedtke R, van Wijk R. Differential effects of relaxation techniques on ultraweak photon emission. J Altern Complement Med 2008a; **14**: 241-250.
209 van Wijk R, van Wijk EP, Wiegant FA, Ives J. Free radicals and low-level photon emission in human pathogenesis: State of the art. Indian J Exp Biol 2008b; **46**: 273-309.
210 Voelcker-Rehage C, Godde B, Staudinger UM. Activity, physical and psychological mobility in old age. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2006; **49**: 558-566.
211 Wiegant FA, Spieker N, van der Mast CA, van Wijk R. Is heat shock protein re-induction during tolerance related to the stressor-specific induction of heat shock proteins? J Cell Physiol 1996; **169**: 364-372.
212 Willner P, Healy S. Decreased hedonic responsiveness during a brief depressive mood swing. J Affect Disord 1994; **32**: 13-20.
213 Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, Nichols-Larsen D. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 2006; **296**: 2095-2104.
214 Yu B, Becnel J, Zerfaoui M, Rohatgi R, Boulares AH, Nichols CD. Serotonin 5-hydroxytryptamine(2A) receptor activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency. J Pharmacol Exp Ther 2008; **327**: 316-323.
215 Zhu W, Cadet P, Baggerman G, Mantione KJ, Stefano GB. Human white blood cells synthesize morphine: CYP2D6 modulation. J Immunol 2005a; **175**: 7357-7362.
216 Zhu W, Ma Y, Bell A, Esch T, Guarna M, Bilfinger TV, Bianchi E, Stefano GB. Presence of morphine in rat amygdala: Evidence for the mu3 opiate receptor subtype via nitric oxide release in limbic structures. Med Sci Monit 2004; **10**: BR433-439.
217 Zhu W, Mantione KJ, Kream RM, Cadet P, Stefano GB. Cholinergic regulation of morphine release from human white blood cells: evidence for a novel nicotinic receptor via pharmacological and microarray analysis. Int J Immunopathol Pharmacol 2007; **20**: 229-237.
218 Zhu W, Mantione KJ, Shen L, Cadet P, Esch T, Goumon Y, Bianchi E, Sonetti D, Stefano GB. Tyrosine and tyramine increase endogenous ganglionic morphine and dopamine levels in vitro and in vivo: cyp2d6 and tyrosine hydroxylase modulation demonstrates a dopamine coupling. Med Sci Monit 2005b; **11**: BR397-404.