Converging Cellular Processes for Substances of Abuse: Endogenous Morphine

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Submitted: 2008-01-15 Accepted: 2008-02-02 Published online: 2008-02-22

Key words: **nicotine; alcohol; cocaine; morphine; drug abuse; nitric oxide; addiction**

Neuroendocrinol Lett 2008; **29**(1):63–66 **PMID:** 18283266 NEL290108A26 © 2008 Neuroendocrinology Letters • **www.nel.edu**

Abstract

Human and invertebrate tissues have the ability to synthesize morphine, making it an endogenous chemical messenger. Given this new insight we sought to investigate whether substances of abuse have the ability to interact with endogenous morphine processes. Moreover we have shown that cocaine, alcohol and nicotine significantly enhance ^{125}I-trace labeled morphine release from invertebrate ganglia and human white blood cells. These data and newer research contribute to an evolving hypothesis linking the reinforcing and addictive properties of a variety of drugs of abuse to convergent mechanisms, involving endogenous morphine signaling and establish an opiate foundation as a unifying principle by which we may advance our understanding of polymodal drug abuse mechanisms.

LETTER

Cocaine and heroin exert extreme control over behavior, while alcohol, nicotine or marijuana does not. Under 'normal' circumstances, abstinence seems to be possible with these substances more easily as indicated by the fact that the latter substances of abuse have become 'socially accepted' in many cultures [1–5]. Additionally personality, social and genetic factors may also play an important role in a substance of abuse's actions [1,6–20]. In regard to alcohol this is especially true, considering wine virtues [21]. Addiction, therefore, appears to be a loss of control over pleasurable and biologically useful events ('healthy drug use'), turning a positive motivation into a disaster [8,22–24]. We surmise this may be due to the fact morphine appears to be the "bottle-neck" reaction for substances of abuse as hypothesized by Stefano and colleagues [25,26].

Caffeine, alcohol and nicotine, given as examples, all activate brain reward pathways directly. Some of these drugs are known for their recreational use, involving, for instance, desirable psychological effects, such as relaxation and stress reduction [8,10,27]. Various addictive drugs share the common feature of stimulating the same dopaminergic brain reward system. For example, heroin enhances dopamine levels by increasing dopamine release, whereas cocaine inhibits dopamine reuptake. These actions has been related to their appetitive motivational effects [1,6,28].

Recently, normal healthy human white blood cells and invertebrate neural tissues were found to have the ability to synthesize morphine, opening up a new world of comprehension concerning endogenous morphine processing and signaling [29–32]. Human morphine synthesis was, as

expected, dependant on its precursors, L-DOPA, reticuline, THP and tyramine, in a concentration-dependent manner [29]. Furthermore, CYP2D6 appears to be a major enzyme regulating this pathway [29,30,33–38]. Importantly, it is noted that dopamine is a morphine precursor [31,32].

In a somewhat parallel story with opiate alkaloid induced addiction [30], nicotine also addictive [39], significantly enhanced ^{125}I-trace labeled morphine released from invertebrate ganglia into the extracellular medium in a concentration dependent manner as did alcohol [40]. This also occurs in human white blood cells [41–43], suggesting that nicotine's and alcohols effects occur via an enhancement of endogenous morphine's signaling. Nicotine's and alcohols addictive properties may arise from this ability to enhance endogenous morphine levels, opening up a new level of understanding in substance induced addiction and behavioral effects as well as morphine regulation.

Regarding alcohol, supporting this conclusion are the studies that demonstrate alcohol is addicting and interacts with the reward system of the human brain, including exogenous morphine actions [44–48]. We surmise ethanol's addicting and short pleasure-promoting properties may be related to its morphine enhancing effect and its depressing effect to reducing neural morphine levels.

Not surprisingly, cocaine also exerts its mechanism of action via the alteration of dopaminergic processes [49]. In both invertebrates and mammals cocaine inhibits the ability to reuptake released dopamine via blocking its transporter, allowing more dopamine to be present for signaling [50,51]. We surmise that this dopamine may in time be channeled to the morphinergic system whereby morphine activity is enhanced. Furthermore, as recently demonstrated in invertebrate and human tissues cocaine promotes a statistically significant enhancement of ^{125}I-trace labeled morphine release[40], which also occurs in human white blood cells [41], suggesting that cocaine's effect, in part, may occur via an enhancement of endogenous morphine's signaling.

The brain's reward and motivation circuitry with its limbic components represents the crucial neurobiological system underlying pleasure phenomena [8,10,11,30–24,52–59]. It not only serves pleasure and motivation, but also involves aspects of behavior, reproduction and sexual activity, emotion, belief and trust, memory, cognition, stress physiology and autonomic functions, relaxation and well-being – to name a few [7,8,10,60,61]. Neurotransmitters potentially acting on CNS structures are, for example, dopamine, GABA, glutamate, serotonin, acetylcholine, morphine, nitric oxide, noradrenaline, cortisol as well as endocannabinoids.

Natural rewards can be modulated by the activity of the brain's reward and motivation circuitry. Feeding, sexual activity or maternal behavior can be facilitated each by opiate activation of the reward system [9,62–64]. The VTA (i.e., ventral tegmental dopamine system) seems to provide an important neurochemical interface where exogenous opiates and endogenous opioid peptides can activate a CNS mechanism involved in appetitive motivation and reward [1,8]. Obviously, endogenous morphinergic signaling may also play a role [31,54,58]. This is especially true since endogenous morphine biosynthesis may involve elements of dopamine metabolism [29,30,33,65], linking two signaling systems. Additionally, endogenous morphine has been found in hippocampal tissues [66,67] and morphinergic signaling has been demonstrated to release constitutive nitric oxide here [68], linking morphine to limbic structures and nitric oxide effects. Thus, the VTA serves as a appetitive motivation system for diverse behaviors, since it controls both normal and pathological behaviors [1,8,69,70].

Artificial rewards and drugs, in contrast to natural stimuli that work, for example, by moderate sensory organ stimulation, are capable of acting directly on VTA and nucleus accumbens pathways, allowing only little flexibility and modulation to interfere (see above). Consequently, artificial rewards can diminish self-control and beneficial motivational behavior, leading to a potentially dangerous or detrimental outcome, i.e., motivational toxicity [1]. They may therefore be considered biologically senseless.

Moreover, reward substrates that directly act on the brain's reward pathways are more potent than other rewards, such as food or water: subjects prefer to choose self-imposed starvation when forced to make a choice between obtaining food and water or direct electrical stimulation of the reward circuitry [1,71,72]. We can assume that nature has not made preparation, that is, has not planned for this artificial short-cut to occur. The psychiatric implications of this system have been examined as well, including brain reward circuitry [8,73–75]. Interestingly, with this link we find a strong connection or convergence of neurobiology, i.e., substances of abuse, endogenous morphine, with behavior, i.e., addiction and pleasure/reward behaviors, and yet, with disease states. Thus, these data and newer research contribute to an evolving hypothesis linking the reinforcing and addictive properties of a variety of drugs of abuse to convergent mechanisms involving endogenous morphine signaling and establish an opiate foundation as a unifying principle by which we may advance our understanding of polymodal drug abuse mechanisms.

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