Neuroendocrinology Letters Volume 28 No. 6 2007

ORIGINAL ARTICLE

The immune effects of TRYCATs (tryptophan catabolites along the IDO pathway): Relevance for depression – and other conditions characterized by tryptophan depletion induced by inflammation

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Submitted: October 21, 2007 *Accepted: November 18, 2007*

Key words: **tryptophan; indoleamine (2,3)-dioxygenase (IDO); kynurenine; kynurenic acid; xanthurenic acid; quinolinic acid; inflammation; depression; anxiety; interferon**

Neuroendocrinol Lett 2007; **28**(6):826–831 **PMID:** 18063923 NEL280607A11

Abstract

Immune activation is accompanied by induction of indoleamine (2,3)-dioxygenase (IDO), an enzyme which degrades tryptophan, a phenomenon which plays a role in the pathophysiology of major depression and post-natal depression and anxiety states. TRYCATs – tryptophan catabolites along the IDO pathway – such as kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid, have multiple effects, e.g. apoptotic, anti- versus pro-oxidant, neurotoxic versus neuroprotective, and anxiolytic versus anxiogenic effects. The aim of the present study was to study the immune effects of the above TRYCATS.

Toward this end we examined the effects of the above TRYCATs on the LPS + PHA-induced production of interferon-γ (IFNγ), interleukin-10 (IL-10), and tumor necrosis factor-α (TNFα) in 18 normal volunteers.

We found that the production of IFNγ was significantly decreased by all 4 catabolites. Xanthurenic acid and quinolinic acid decreased the production of IL-10. Kynurenine, kynurenic acid, and xanthurenic acid, decreased the IFNγ/IL-10 production ratio, whereas quinolinic acid increased this ratio. Kynurenic acid significantly reduced the stimulated production of TNFα.

It is concluded that kynurenine, kynurenic acid, and xanthurenic acid have anti-inflammatory effects trough a reduction of IFNγ, whereas quinolinic acid has pro-inflammatory effects in particular via significant decreases in IL-10. Following inflammation-induced IDO activation, some TRYCATs, i.e. kynurenine, kynurenic acid, and xanthurenic acid, exert a negative feedback control over IFNγ production thus downregulating the initial inflammation, whereas an excess of quinolinic acid further aggravates the initial inflammation.

INTRODUCTION

Major depression, and postnatal depressive and anxiety states are accompanied by a) changes in the metabolism of serotonin (5-HT), such as decreased serum tryptophan, and b) immune activation, as indicated by – amongst other things – increases in pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1, interferon-γ (IFNγ) and tumor necrosis factor-α (TNFα) [1–8]. As explained previously [9,10], the lowered tryptophan availability in depression is probably the consequence of activation of the inflammatory response system. Indeed, depression is accompanied by elevated levels of neopterin and IFNγ and by lowered plasma L-tryptophan (L-TRP) [3]. In depressed patients, we found significant interrelationships between the lowered availability of plasma tryptophan and signs of immune activation [2,3,11]. This was explained by the effects of the pro-inflammatory cytokines inducing indoleamine-2,3 dioxygenase (IDO), an enzyme involved in tryptophan degradation [2,3,5,6,11].

IDO is an intracellular heme-containing enzyme that catalyzes the initial and rate-limiting step in tryptophan degradation along the so-called IFNγ / IDO dependent pathway. IDO is widely expressed in a variety of human tissues, such as the brain, kidney, lung, spleen, and duodenum, as well as in macrophages and dendritic cells [12–14]. IDO is induced in inflammatory states by pro-inflammatory cytokines, the most important being IFNγ, although also IL-1 and TNFα, may enhance IDO at least synergistically with IFNγ [15,16]. Upon IDO activation, tryptophan is degraded along the kynurenine pathway and various metabolites are formed, such as kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid. These substances – which we label as TRYCATs (tryptophan catabolites among the IDO pathway) – have multiple effects since they are neurotoxic or neuroprotective and may induce apoptosis, act as pro- or anti-oxidants, and are anxiolytic or anxiogenic [17,18]. However, the effects of the different TRYCATs on the production of pro- and anti-inflammatory effects are not known.

The aim of the present study was to examine the immunoregulatory effects of the TRYCATs, kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid. Toward this end we examined the ex vivo effects of those TRYCATs on the stimulated production of IFNγ, IL-10 and TNFα.

SUBJECTS AND METHODS

Subjects

After an overnight fast, blood was drawn from 18 healthy volunteers (9 males and 9 females, mean age = 31.2±4.2 years) between 8:30 and 9:30 a.m. All subjects gave written informed consent after full explanation of the study design. We excluded the following subjects: i) age under 18 or over 40; ii) a past or present history of psychiatric disorders (axis-I); iii) subjects who ever had been taken major psychotropic medication, such as antidepressants, antipsychotics and anxiolytics and subjects with alcohol or any other drug of dependence abuse; iv) subjects with any organic disorder, such as diabetes, autoimmune diseases, cardiovascular disorders; v) smokers; vi) subjects who suffered from an infectious, allergic or inflammatory response for at least 2 weeks prior to blood sampling. The subjects abstained from caffeine and alcohol for at least 12 hours prior to blood sampling.

Methods

The effects of kynurenine, kynurenic acid, xanthurenic acid, and quinolinic acid on the production of IFNγ, TNFα and IL-10, were examined by stimulating diluted whole blood with PHA and LPS. Blood was diluted four times in RPMI 1640 culture medium (BioWhittaker, Verviers, Belgium) supplemented with L-glutamine and antibiotics (100 U/ml penicilline and 100 µg/ml streptomycine). The suspension was homogenized and plated in a 24-well tissue culture plates (Costar, The Netherlands) at 1 ml/well. After the addition of the 0.25 ml blood suspension, the plates were incubated for 30 min at 37 °C and 5% CO_2. The TRYCATs (Sigma-Aldrich, Bornem, Belgium) were dissolved in sterile medium, whereas medium alone served as the corresponding control. 0.25 ml of whole blood from each of the volunteers was cultured with 4 mediums alone (in order to have 4 control conditions for optimal use of the statistical analyses) with 4 concentrations of each of the TRYCATs. 20 µl of each of the concentrated solutions of the TRYCATs were added to the wells and gently mixed with the medium. The final concentrations yielded kynurenine 2 µM, 4 µM, 8 µM and 20 µM; kynurenine acid 70 nM, 140 nM, 280 nM and 700 nM, quinolinic acid 250 nM, 500 nM, 1000 nM and 2500 nM, and xanthurenic acid 5 µM, 10 µM, 20 µM and 40 µM. We decided to employ these TRYCAT concentrations because these are the concentrations reached in blood-brain during physiological and pathophysiological conditions. The plates were placed on a gyratory shaker for 10 min to mix to contents of the wells, and afterwards incubated for 20 min at 37°C and 5% CO_2. Then, the cultures were stimulated with LPS (5 µg/ml; *E. coli* 026:B6; lyophylized and sterilized by gamma-irradiation; Sigma, Belgium) and and PHA (1 µg/ml; Murex Diagnostics Ltd, Dartford, England). Plates were mixed for 10 min and transferred to the incubator. Supernatant for the assay of TNFα was collected after 24 h; and a supernatant for the measurement of IFNγ and IL-10 was collected after 72 h. After incubation, the plates were mixed for 10 min. before centrifugation at 800×g and 41 °C for 15 min. Supernatants were carefully aspirated and transferred to labeled eppendorf tubes. Samples were stored at –20 °C until assayed for cytokines.

Cytokines were determined using commercially available enzyme linked immunosorbent assays (ELISA) from NIBSC (IFNγ assays) and BD, OptEIA™ ELISA Sets (TNFα and IL-10 assays). All assays were performed

according to the manufacturer instructions. Determinations were performed in a single run by the same operator (IM). The intra-assay variations were lower than 8% for all assays.

Statistics

We employed repeated measure (RM) design analyses of variance (ANOVAs) to examine the within-subject variability with the 4 positive controls and the each of the 4 TRYCATs at 4 different concentrations. When the overall within-subject analysis yielded significant results, we used simple effects in order to examine the differences in the production of cytokines between the positive control and each of the 4 concentrations of the TRYCATs. The IFNγ/IL-10 ratio was computed as: square-root transformed IFNγ / square-root transformed IL-10. ANOVAs were employed to ascertain differences between group means. Relationships between variables were assessed by means of Pearson's product moment correlation coefficients.

RESULTS

Table 1 shows the effects of the TRYCATs on the production of IFNγ. Kynurenine significantly suppressed the production of IFNγ; this suppression was significant at 4 μM (F=5.9, df=1/68, p=0.02) and 8 μM (F=14.3, p=0.0006) and showed a trend toward significance at 20 μM (F=3.8, df=1/68, p=0.053). Kynurenine acid significantly reduced the production of IFNγ; this was significant at 70 nM (F=7.3, p=0.009); 140 nM (F=8.1, p=0.006); and 280 nM (F=34.2, $p<10^{-4}$). Quinolinic acid significantly reduced the production of IFNγ and this was significant at 2500 nM (F=3.9, p=0.04). Xanthurenic acid had a significant suppressant effect on IFNγ. Inspection of the molar concentrations of xanthurenic acid showed that xanthurenic acid yielded significant effects at 5 μM (F=5.5, p=0.02); 10 μM (F=8.4, p=0.005); and 20 μM (F=3.8, p=0.05).

Table 2 shows the effects of the TRYCATs on the production of IL-10. Kynurenine and kynurenine acid did not have any sigificant effect on the production of IL-10. Quinolinic acid significantly reduced the production of IL-10; this effect was significant at 250 nM (F=10.8, p=0.002), 500 nM (F=12.0, p=0.001), and 1 000 nM (F=7.8, p=0.007); there was a trend toward a significance at 2 500 nM (F=3.8, p=0.052). Xanthurenic acid suppressed the production of IL-10 at 5 μM (F=5.5, p=0.02), 10 μM (F=8.4, p=0.005) and 20 μM (F=3.9, p=0.05).

Table 3 shows the effects of the TRYCATs on the production ratio IFNγ/IL10. Kynurenine significantly suppressed the production ratio; this suppression was significant at 20 μM (F=7.4, p=0.008). Kynurenine acid significantly reduced the production ratio IFNγ/IL-10 and

Table 1. Effects of the the TRYCATs on the production of interferon-γ.

condition	C1	C2	C3	C4	F	p-value
control	1618 (1131)	1514 (956)	1539 (998)	1511 (902)	–	–
kynurenine	1323 (835)	1066 (790)	844 (614)	1155 (881)	23.8	0.00005
kynurenic acid	1325 (899)	1205 (914)	905 (644)	1475 (1027)	34.5	0.00001
quinolinic acid	1392 (790)	1469 (1136)	1320 (718)	1294 (888)	7.2	0.009
xanthurenic acid	1155 (881)	941 (812)	1150 (847)	1370 (1013)	15.6	0.0004

All results are shown as mean (± SD) and in pg/ml. All results of RM design ANOVAs with the control condition and the 4 concentrations (C1–C4) of each of the TRYCATs as repeated measurements (all df=1/68).
C1–C4: kynurenine: C1=2 μM, C2=4 μM, C3=8 μM and C4=20 μM; kynurenic acid: C1=70 nM, C2=140 nM, C3=280 nM and C4=700 nM; quinolinic acid: C1=250 nM, C2=500 nM, C3=1 000 nM and C4=2 500 nM; and xanthurenic acid: C1=5 μM, C2=10 μM, C3=20 μM and C4=40 μM.

Table 2. Effects of the the TRYCATs on the production of interleukin-10.

condition	C1	C2	C3	C4	F	p-value
control	1992 (1254)	1997 (1080)	1886 (1015)	1941 (1103)	–	–
kynurenine	1922 (899)	1838 (1024)	1741 (919)	1680 (1279)	3.1	0.08
kynurenic acid	1545 (1194)	1962 (1110)	1893 (1076)	1799 (1024)	3.6	0.06
quinolinic acid	1492 (880)	1470 (817)	1463 (994)	1645 (1138)	33	0.00001
xanthurenic acid	1874 (1456)	1659 (1032)	1721 (949)	1811 (1323)	6.7	0.01

All results are shown as mean (± SD) and in pg/ml. All results of RM design ANOVAs with the control condition and the 4 concentrations (C1–C4) of each of the TRYCATs as repeated measurements (all df=1/68).
C1–C4: kynurenine: C1=2 μM, C2=4 μM, C3=8 μM and C4=20 μM; kynurenic acid: C1=70 nM, C2=140 nM, C3=280 nM and C4=700 nM; quinolinic acid: C1=250 nM, C2=500 nM, C3=1 000 nM and C4=2 500 nM; and xanthurenic acid: C1=5 μM, C2=10 μM, C3=20 μM and C4=40 μM.

Table 3. Effects of the the TRYCATs on the interferon-γ / interleukin-10 production ratio.

condition	C1	C2	C3	C4	F	p-value
control	0.99 (0.51)	0.96 (0.52)	1.00 (0.58)	0.99 (0.51)	–	–
kynurenine	0.92 (0.61)	0.82 (0.48)	0.69 (0.33)	1.02 (0.81)	4.6	0.03
kynurenic acid	1.08 (0.63)	0.86 (0.61)	0.71 (0.37)	1.01 (0.57)	4.4	0.03
quinolinic acid	1.08 (0.47)	1.10 (0.59)	1.13 (0.58)	1.03 (0.55)	9.3	0.004
xanthurenic acid	0.87 (0.57)	0.76 (0.38)	0.87 (0.43)	0.97 (0.54)	7.3	0.009

All results are shown as mean (± SD) and in pg/ml. All results of RM design ANOVAs with the control condition and the 4 concentrations (C1–C4) of each of the TRYCATs as repeated measurements (all df=1/68).
C1–C4: kynurenine: C1=2 μM, C2=4 μM, C3=8 μM and C4=20 μM; kynurenic acid: C1=70 nM, C2=140 nM, C3=280 nM and C4=700 nM; quinolinic acid: C1=250 nM, C2=500 nM, C3=1 000 nM and C4=2 500 nM; and xanthurenic acid: C1=5 μM, C2=10 μM, C3=20 μM and C4=40 μM.

Table 4. Effects of the the TRYCATs on the production of tumour necrosis factor-α.

condition	C1	C2	C3	C4	F	p-value
control	2022 (1078)	1966 (1176)	2018 (1116)	2068 (1165)	–	–
kynurenine	2027 (1163)	1970 (1145)	1835 (1067)	1935 (1200)	2.1	0.1
kynurenic acid	2038 (1237)	1726 (1192)	1374 (1051)	1958 (1125)	21.4	0.00009
quinolinic acid	2172 (1283)	2117 (1170)	1992 (1044)	2261 (1137)	3.7	0.06
xanthurenic acid	2219 (1074)	1948 (1196)	1877 (1131)	1765 (1157)	1.8	0.2

All results are shown as mean (± SD) and in pg/ml. All results of RM design ANOVAs with the control condition and the 4 concentrations (C1–C4) of each of the TRYCATs as repeated measurements (all df=1/68).
C1–C4: kynurenine: C1=2 μM, C2=4 μM, C3=8 μM and C4=20 μM; kynurenic acid: C1=70 nM, C2=140 nM, C3=280 nM and C4=700 nM; quinolinic acid: C1=250 nM, C2=500 nM, C3=1 000 nM and C4=2 500 nM; and xanthurenic acid: C1=5 μM, C2=10 μM, C3=20 μM and C4=40 μM.

this effect was significant at 280 nM (F=18.0, p=0.0002). Quinolinic acid significantly increased the IFNγ/IL-10 production ratio and this effect was significant at 500 nM (F=4.2, p=0.04); there were trends to significant effects at 250 nM (F=2.8, p=0.09), and 1000 nM (F=3.2, p=0.07). Xanthurenic acid induced a significant suppressant effect on the IFNγ/IL-10 production ratio.

Table 4 shows the effects of the TRYCATs on the production of TNFα. Kynurenine, quinolinic acid and xanthurenic acid did not have any significant effects of the production of TNFα. Kynurenine acid significantly reduced the production of TNFα and this effect was significant at 140 nM (F=5.1, p=0.02) and 280 nM (F=37.2, $p<10^{-4}$).

There were no significant differences between men and women in any of the cytokines and no significant correlations with age.

DISCUSSION

The major finding of this study is that the TRYCATs have significant mediating effects on pro- and antiinflammatory cytokines. Thus, all 4 TRYCATs decreased the production of IFNγ, kynurenic acid significantly reduced TNFα, whereas xanthurenic acid and quinolinic acid decreased the production of IL-10. Overall, kynurenine, kynurenic acid, and xanthurenic acid decreased the IFNγ/IL-10 production ratio, whereas quinolinic acid increased this ratio. Thus, kynurenine, kynurenic acid, and xanthurenic acid have anti-inflammatory effects, whereas quinolinic acid appears to have pro-inflammatory effects.

Our results show that induction of IDO by inflammatory signals partly determines the fate of the inflammatory process not only through the induction of tryptophan depletion, but also by the formation of the TRYCATs, which modulate the production of cytokines. Our results suggest that kynurenine, kynurenic acid, and xanthurenic acid exert a negative feedback control over the inflammation-induced IFNγ production and that quinolinic acid may further aggravate the initial inflammation. Thus, depending on the TRYCATs formed during an immune response the initial immune response may be downregulated through tryptophan depletion and the formation of the above 3 TRYCATs or may be further upregulated when an excess of quinolinic acid is formed. Here, differences in enzyme repertoires in different cell types are important. Astrocytes, for example, lack kynurenine hydroxylase so that large amounts of kynurenine are produced after stimulation by pro-inflammatory cytokines, whereas only minor amounts of quinolinic acid are formed [19]. Therefore, in astrocytes the TRY-

CATs induced through inflammation may downregulate the initial inflammatory response. In this respect, it was hypothesized that induction of local IDO expression initiates a negative feedback loop which may underlie the self-limitation of autoimmune inflammation during neurologic disorders [20]. In the presence, however, of macrophages or microglia, kynurenine – synthesized by the astroglia – is metabolized into quinolinic acid [19] and thus the pro-inflammatory effects of quilolinic acid may prevail and thus aggravate the initial inflammatory response.

The findings of the present study show that the immunoregulatory effects of the TRYCATs should be taken into account when considering their other functions, e.g. the induction of apoptosis, their activity as pro-oxidants, and their neurotoxic or neuroprotective effects [17,18]. Indeed, kynurenine and quinolinic acid are neurotoxic and preconvulsive [17] and may be related to the pathophysiology of neurodegenerative disorders [21,22]. Kynureninic acid, on the other hand, is a neuroprotectant [18]. Part of the neurotoxic effects of quinolinic acid may be caused through its pro-oxidative effects, which may induce lipid peroxidation [23]. Moreover, quinolinic acid may produce overstimulation of hippocampal N-methyl-D-aspartate (NMDA) receptors, which leads to apoptosis and hippocampal atrophy [24]. Previously, we have reviewed that – in depression – increased quinolinic acid formation may play a role in the NMDA overstimulation and in neurodegeneration [25,26,27]. The present results suggest that quinolinic acid through its pro-inflammatory effects may play a role in the pro-oxidative effects and thus in its apoptotic effects.

The findings of the present study are relevant to major depression and postnatal depression and anxiety.

a) Interferon-alpha-based immunotherapy of cancer patients is known to be accompanied by a high frequency of depression and anxiety after starting the treatment. We have shown that higher IFNα induced inflammation is related to: – the development of depression [4,25,26,27]; – IFNα-induced decreases in the availability of tryptophan [4,25,28,29]; – increases in the kynurenine / tryptophan ratio [4]; and – the kynurenine / kynurenic acid ratio [25]. The former ratio reflects IDO activation [4], whereas the latter indicates an increased neurotoxic potential [25]. Both ratios were significantly related to the IFNα-induced severity of depression, suggesting that IFNα-induced depression is not caused by tryptopan depletion as such but by IDO activation causing formation of neurotoxic TRYCATS [4,25,28,29].

b) In the early puerperium, increases in plasma kynurenine and the kynurenine / tryptophan quotient are significantly related to signs of immune activation, such as increased serum IL-6 and IL-8, and to the severity of depressive and anxiety symptoms [5,6]. Kynurenin and quinolinic acid have been demonstrated to be excitatory and to possess anxiogenic activity, whereas TRYCATs with opposite neuroactivities, such as kynurenic acid and xanthurenic acid, have anxiolytic effects and may antagonize the anxiolytic effects of the excitatory TRYCATs and anxiogenic substances, such as caffeine [17,30,31]. The above results may suggest that an increased degradation of tryptophan along the kynurenine pathway, rather than a lowered availability of plasma tryptophan, is related to the occurrence of depressive and anxiety symptoms.

Moreover, the enzyme IDO has a complex role in immunoregulation not only in depression but also in infection, pregnancy, autoimmunity, transplantation, and neoplasia. Thus, the IFNγ / IDO-dependent pathway is associated with chronic inflammation; persistent parasitic; viral; and bacterial infections; tumor growth; and pregnancy [32]. Recent studies have demonstrated a crucial role for tryptophan withdrawal and kynurenine production in the induction of peripheral tolerance, e.g. materno-fetal tolerance, tolerance to tumor antigens, and microbial infections by inducing T cell unresponsiveness [32]. Induction of the IFNγ / IDO dependent pathway in antigen presenting cells correlates with weak T cell proliferation, enhanced apoptosis, and weak responses in vivo [33–35]. It has been shown that local depletion of tryptophan blocks T cell clonal expansion and T cell activation. Indeed, tryptophan depletion prevents entry into the S-phase by inducing cell cycle arrest. Thus, the response to tryptophan withdrawal is not simply metabolic shutdown or starvation, but an active, regulated and specific signaling pathway. In addition, the production of the pro-apoptotic TRYCATs, such as quinolinic acid, may cause depletion of specific thymocyte subsets and Th-1 lymphocyte subsets, and, therefore, may cause selective depletion of T lymphocyes [36].

In summary, kynurenine, kynurenic acid, and xanthurenic acid have anti-inflammatory effects, whereas quinolinic acid has pro-inflammatory effects. These effects are relevant for each condition which involves induction of IDO and thus the formation of the TRYCATs.

ACKNOWLEDGEMENTS

The research reported was supported by a NARSAD Distinguished researcher award to M.Maes and by M-CARE4U and CRC-MH, Antwerp, Belgium.

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