Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neuroscience Letters 365 (2004) 106–110
Neuroscience Letters
www.elsevier.com/locate/neulet

Intranasal administration of human IL-6 increases the severity of chemically induced seizures in rats

Allan V. Kalueff [a,b,*], Kai A. Lehtimaki [b], Aarne Ylinen [b], Jari Honkaniemi [b], Jukka Peltola [b]

[a] *Medical School, University of Tampere, Tampere 33014, Finland*
[b] *Department of Neurology and Rehabilitation, Tampere University Hospital, Tampere 33512, Finland*

Received 16 February 2004; received in revised form 8 April 2004; accepted 26 April 2004

Abstract

Here we study the role of a pleiotropic pro-inflammatory cytokine, interleukin-6 (IL-6), in epilepsy. To examine this problem, we used human recombinant IL-6 applied intranasally (400 ng/40 μl) to rats 1 h before seizures induced by systemic injection of pentylenenetrazole (PTZ, 75 mg/kg). Overall, compared to the saline-treated control animals ($n = 11$ in each group), IL-6-treated rats demonstrated elevated levels of IL-6 in the frontal lobe (measured by ELISA) and increased severity of PTZ-induced seizures (shorter latency, longer duration and higher mortality). Our findings show that IL-6 plays a pro-convulsant role in the brain and suggest that the IL-6 system may be a novel target for the development of anticonvulsant drugs.

Keywords: IL-6; Epilepsy; Intranasal administration; Chemically induced seizures; Rat

A pleiotropic cytokine interleukin-6 (IL-6) is involved in inflammatory processes as a systemic mediator of the acute phase response in infection [10,18]. IL-6 has been found in the brain, including neuronal, glial and microglial cells [18,27], where it plays an important modulatory and neuroprotective role [5,27]. IL-6 influences mesocorticolimbic dopamine and serotonin neurotransmission and also has activating effects on locomotion [35–37]. Recently IL-6 was reported to have neurotoxic effects and has also been suggested to play a significant role in various diseases of the central nervous system [5,26]. There is a growing body of evidence linking IL-6 to epilepsy [26,27]. Seizures are a common complication in patients with infectious diseases accompanied by elevated plasma and brain IL-6 levels [10,12–14]. Elevated levels of IL-6 occur in the plasma and cerebrospinal fluid of patients with recent epileptic seizures, where the levels of IL-6 generally correlate with the severity of the seizures [16,17,21–23]. These elevated IL-6 levels were observed in patients without any infection or brain trauma, and are most likely a consequence of neuronal epileptic activity associated with seizures [21–23]. In rodents, limbic seizures rapidly and transiently enhanced IL-6 in the hippocampus [6,33]. Elevated IL-6 levels are seen after in vivo administration of excitatory amino acids [20]. Neuronal depolarisation and Ca^{2+} influx have been shown to directly activate production of IL-6 in the neuronal cells in vitro [26]. Finally, transgenic mice over-expressing IL-6 in the brain develop spontaneous behavioural seizures, increased hippocampal excitatory activity and increased sensitivity to glutamatergic-induced seizures [4,27,31].

However, the role of IL-6 in epilepsy is still unclear and thus needs further experimental investigation. In the present study, we directly examined the effects of IL-6 on chemically induced seizures. In order to minimise pyrogenic and other unwanted side effects of IL-6, and since this cytokine penetrates the blood–brain barrier poorly, we used intranasal administration shown to be effective in by-passing the blood–brain barrier for several other cytokines and similar polypeptides [7,9,15,19]. Since rat and human IL-6 possess a high degree of homology, we chose to use human recombinant IL-6 (hIL-6) for our experiments. Since our work is the first study to use IL-6 intranasally, we used 400 ng IL-6 for our studies, basing our choice on recent data [36,37] showing that at this dose IL-6 is able to cause central effects in rats following systemic administration. Choosing the pretreatment time for our studies, we

* Corresponding author. Tel.: +358-3-2156640; fax: +358-3-2156170.
E-mail address: avkalueff@inbox.ru (A.V. Kalueff).

0304-3940/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.neulet.2004.04.061

considered recent findings showing that (i) cytokine-like molecules may appear in the brain within 20–30 min following their intranasal administration [7,19] and (ii) IL-6 can cause its central effects 30–60 min following its systemic administration [36,37]. As such, 1 h pretreatment time seemed appropriate for IL-6 at this dose to reach the brain and affect seizures. Here we demonstrate that intranasally administered hIL-6 appears in the brain and leads to increased severity of seizures and higher mortality in the model of pentylenetetrazole (PTZ)-induced seizures in rats.

Twenty two adult male Wistar rats (220–240 g; University of Tampere, Finland) were maintained in a standard virus/parasite-free facility and exposed to a 12 h/12 h light–dark cycle. Lights were turned off at 18:00 and on at 06:00 h. The animals were experimentally naïve and housed in pairs, with food and water freely available. The testing was always conducted between 14:00 and 18:00 h. On the days of the experiments animals were brought individually into the experiment room and immobilised in a vertical position, head up, for 5 min in a specially designed plastic restraint box. HIL-6 purchased from R&D Systems (USA; 10 μg diluted in 1 ml of sterile isotonic saline) was used in this study. Intranasal administration was performed in immobilised unanaesthetised animals using a 40 μl micropipette (Labsystems, Finland). Each animal received 10 μl of hIL-6 or isotonic saline at once in each nostril. This treatment was repeated after a 3-min interval (total amount administered was 400 ng/40 μl/rat). After the intranasal administration procedure the animals were returned to their cages for recovery. One hour later, each animal received a bolus of intraperitoneal injection of PTZ (Sigma, UK; 75 mg/kg) and was placed in a new clean cage for observation of seizure profile. Seizures and seizure latency times were observed visually over a 30-min observation period by a trained experimenter blind to the treatment groups. The following parameters were recorded: the time to onset of the first twitch; the number of rats having motor seizures; the duration of the ofo-facial, clonic and tonic components of seizures; the mortality rate. The intensity of seizures was registered using a modified Racine's scoring system [25]: 0 (no response), 1 (freezing), 2 (head nodding or isolated twitches), 3 (oro-facial seizure), 4 (clonic seizure), 5 (tonic seizure), 6 (death). Clonic seizures consisted of rhythmic contractions of forelimbs and/or hindlimbs. Tonic seizures consisted of rigid extension of the fore- and/or hindlimbs with or without posture loss. An animal was considered dead if the heart was not beating upon manual check. Following decapitation, brains were removed and dissected on a cold plate. Frontal lobes (anterior to optic chiasma) were isolated and stored at −70 °C until the time of assay. Samples were weighted and homogenised in 50 mM PBS (pH = 7.5) using a Potter homogeniser. Thereafter, they were centrifuged for 15 min (5000 rpm) and supernatant was removed and stored. Commercial ELISA kit (R&D Systems, USA) was used to measure the level of hIL-6 in the frontal lobe of the brain. Animal care and experimental procedures were conducted in accordance with the European legislation and the guidelines of the National Institutes of Health. All animal experiments reported here were approved by the Ethical Committee of the University of Tampere. All results are expressed as means ± S.E.M. Data were analysed by Student's *t*-test for independent samples. A probability of less than 0.05 was considered statistically significant.

The results of the present study are summarised in Table 1. Overall, hIL-6 produces a dramatic increase in seizure severity in PTZ-treated rats. While the duration of relatively mild oro-facial seizures was similar in both groups (Table 1), the duration of more severe clonic/tonic components and the total duration of seizures were almost double in rats treated with hIL-6. Also, there was a significantly shorter latency to the first twitch (Table 1). Mortality rate (55%) was almost 3-fold higher in the hIL-6-treated group (18%), although not significantly. Analysis of ELISA data shows that intranasal administration of hIL-6 results in a significant increase in IL-6 levels in frontal lobe (18.6 ± 5.4) compared to (2.2 ± 0.6) in saline-treated controls ($P < 0.05$), thus, correlating with an increased severity of seizures. Together, these data clearly indicate a pro-convulsant effect of exogenously applied hIL-6 in the brain following intranasal administration in a model of PTZ-induced seizures.

In general, our findings are the first data that directly link exogenous IL-6 to increased seizure severity in rats. The chemoconvulsant drug PTZ used in the present study to induce seizures, is known to act in the brain through inhibition of gamma-aminobutyric acid (GABA) [29]. Many drugs that act on the GABAergic system are able to affect IL-6. For example, the antiepileptic drug sodium valproate, a stimulator of GABAergic transmission, inhibits IL-6

Table 1
Increased susceptibility to PTZ-induced seizures in rats treated with intranasal human IL-6

Group	Number of rats with seizures					Onset of the first twitch (s)	Seizure duration (s)		
	TW	O	C	T	D		O	C/T	Total
Saline	10/11	11/11	7/11	7/11	2/11	417 ± 59	9 ± 3	27 ± 6	36 ± 7
IL-6	9/11	10/11	10/11	9/11	6/11	260 ± 56*	8 ± 3	51 ± 8*	59 ± 10*

TW, twitches; O, oro-facial seizures; C, clonus; T, tonus; C/T, clonic or tonic seizures; D, death. Data are the means ± S.E.M. Fractions represent the number of rats showing different stages of seizures of the total number of rats. The onset of the first twitch was reckoned as 1800 s (total observation time) in the rats not showing this behaviour.

* $P < 0.05$ by *t*-test vs. saline control rats.

synthesis in several human cell lines [1,12]. The anticonvulsant GABA-A agonist muscimol, injected into the brain, inhibits stress-induced elevation of plasma IL-6 [30]. Anticonvulsant benzodiazepines, known to stimulate GABA-A receptors, inhibit the ability of peripheral blood monocytes to synthesise IL-6 both in humans and mice [8] and decrease the secretion of IL-6 in human prostate cancer cells [1]. In contrast, GABA-A antagonists, such as SR-95531, increase both the basal and the restraint stress-induced plasma IL-6 levels [30]. This therefore demonstrates a clear negative correlation between GABAergic activity and IL-6 production. Although the biological meaning of this correlation has yet to be investigated, its existence confirms the interplay between the GABAergic and IL-6 systems. In line with this, a preferential neuronal localisation of IL-6 in GABAergic neurons of the basal forebrain—an area actively involved in epilepsy pathogenesis—has recently been demonstrated [18]. Clearly, some other brain neurotransmitters, including glutamatergic and mesocortical dopaminergic systems, may also be involved in the modulation of IL-6 action and epileptogenesis [27,35]. However, the important role of the GABAergic system in controlling seizure [29], and the link between GABA- and IL-6-related brain mechanisms may explain why IL-6 exacerbates PTZ-induced seizures.

Considering the existing data linking the IL-6 system to epilepsy, one can argue that IL-6 synthesis may represent a compensatory pathway activated after seizures in order to protect the brain, as does, for example, a well-studied anticonvulsant cytokine IL-1Ra [6,16,32]. However, two other cytokines, IL-1β and TNFα, are also elevated after seizures along with IL-6 and IL-1Ra [11,16]. These cytokines both possess inflammatory and pro-convulsant properties [28,32–34] and are known to stimulate the expression of IL-6 [26]. Furthermore, analysis of the time course of cytokine release after seizures shows that increase was first seen in pro-inflammatory convulsant cytokines IL-6, IL-1β and TNFα, while anti-inflammatory anticonvulsant cytokine IL-1Ra peaked much later [6,11,33]. Taken together, these observations indicate that IL-6 release after seizures resembles more that of IL-1β and TNFα, than of IL-1Ra, and are in line with the hypothesis linking pro-inflammatory cytokines to epilepsy. It is therefore no surprise that many anti-inflammatory drugs generally have anticonvulsant effects. Thus, these findings give additional support to the pro-convulsant mode of action of IL-6 in the brain suggested in our study.

However, there are also data in the literature showing some anticonvulsant potential of IL-6. For example, IL-6 enhances expression of brain adenosine A1 receptors known to inhibit neuronal excitation [2] and inhibits the spread of excitation and glutamate release in the somatosensory cortex in rats [5]. Moreover, IL-6 knockout mice were reported to have increased susceptibility to kainic acid-induced seizures [25]. Although these findings may seem to contradict the potential pro-convulsant role of IL-6, their exact mechanisms and biological implication remain unclear. In general, several mechanisms may underlie these conflicting results. First, IL-6 may activate cascades of secondary mechanisms in the brain, some of which may be anticonvulsant. Furthermore, IL-6 may have different actions depending on different experimental models of epilepsy. For example, pro-convulsant effects of IL-6 hyper-production are seen in glutamatergic- but not in cholinergic-induced seizures [27]. In addition, the difference between central versus peripheral site(s) of action for IL-6 may contribute to such conflicting results as suggested by Bluthe et al. [3]. Clearly, such duality in the mechanisms of actions during epilepsy cannot be excluded for IL-6, which already shows dual effects in the brain with both neuroprotective and neurotoxic actions [5,24,26,31]. Furthermore, it will be of interest to examine the effects of intranasally applied IL-6 in epilepsy in more detail, using different doses and pretreatment times, especially (considering the pleotropic nature of IL-6 and multiplicity of its mechanisms of actions) since, like other cytokines [34], IL-6 may have different and even opposite effects at different doses and check-points. It will also be interesting to analyse CSF and plasma levels of IL-6 after intranasal administration, as well as its levels in other parts of the brain (in addition to frontal lobe). Finally, it may be necessary to further assess the role of IL-6 in different models of epilepsy by influencing its physiological effects (for example, blocking them using inhibitors of IL-6 signal transduction or neutralising antiserum). We suggest that such studies may represent very important directions for future research focusing on the role of IL-6 in epilepsy.

In summary, here we have demonstrated a clear pro-convulsant action of exogenously applied IL-6 in rats. Using the intranasal route for IL-6 delivery to the brain, we minimised possible peripheral side effects of IL-6, resolved the problem of by-passing the blood–brain barrier, and assessed the central effects of IL-6 during seizures induced by inhibition of the central GABAergic system. Our data show that intranasally administered hIL-6 (400 ng) leads to a rise in IL-6 levels in the frontal lobe and increases the susceptibility of rats to PTZ-induced seizures. IL-6 affected predominantly the more severe stages of seizures (Table 1), showing the pro-convulsant profile which is clinically relevant and may be of interest for potential application. Importantly, since behavioural activation and epilepsy are based on the same arousal-related neural pathways, the pro-convulsant profile of IL-6 in our study is consistent with earlier data on the general pro-activatory action of IL-6 on behaviour in rats [35–37]. The results of our studies also confirm recent data showing increased sensitivity to glutamatergic-induced seizures in mice with elevated IL-6 levels in the brain [27]. Taken together, these data and those reported here prove that IL-6 has a marked pro-convulsant effect in several experimental models of epilepsy, and may therefore act in the brain as a pro-convulsant cytokine. These findings may point to a new area for the search of novel anti-epileptic drugs based on targeting the central IL-6 system.

Acknowledgements

This study was supported by the Medical Research Fund of Tampere University Hospital and the Centre for International Mobility (CIMO).

References

[1] M. Abdul, N. Hoosein, Inhibition by anticonvulsants of prostate-specific antigen and interleukin-6 secretion by human prostate cancer cells, Anticancer Res. 21 (2001) 2045–2048.
[2] K. Biber, B. Lubrich, B.L. Fiebich, H.W. Boddeke, D. van Calker, Interleukin-6 enhances expression of adenosine A(1) receptor mRNA and signaling in cultured rat cortical astrocytes and brain slices, Neuropsychopharmacology 24 (2001) 86–96.
[3] R.M. Bluthe, B. Michaud, V. Poli, R. Dantzer, Role of IL-6 in cytokine-induced sickness behavior: a study with IL-6 deficient mice, Physiol. Behav. 70 (2000) 367–373.
[4] L. Campbell, R.D. Abraham, E. Masliah, P. Kemper, J.D. Inglis, M.D. Oldstone, L. Mucke, Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6, Proc. Natl. Acad. Sci. U.S.A. 90 (1993) 10061–10065.
[5] G. D'Arcangelo, V. Tancredi, F. Onofri, M. D'Antuono, S. Giovedi, F. Benfenati, Interleukin-6 inhibits neurotransmitter release and the spread of excitation in the rat cerebral cortex, Eur. J. Neurosci. 12 (2000) 1241–1252.
[6] M.G. De Simoni, C. Perego, T. Ravizza, D. Moneta, M. Conti, D. Marchesi, A. De Luigi, S. Garattini, A. Vezzani, Inflammatory cytokines and related genes are induced in the rat hippocampus by limbic status epilepticus, Eur. J. Neurosci. 12 (2000) 2623–2633.
[7] C. Dufes, J.C. Olivier, F. Gaillard, A. Gaillard, W. Couet, J.M. Muller, Brain delivery of vasoactive intestinal peptide (VIP) following nasal administration to rats, Int. J. Pharm. 255 (2003) 87–97.
[8] P. Fruscella, M. Sottocorno, M. Di Braccio, L. Diomede, N. Piccardi, A. Cagnotto, G. Grossi, M. Romano, T. Mennini, G. Roma, 1,5-Benzodiazepine tricyclic derivatives exerting anti-inflammatory effects in mice by inhibiting interleukin-6 and prostaglandinE(2) production, Pharmacol. Res. 43 (2001) 445–452.
[9] V.V. Huber, B.P. Arulanandam, P.M. Arnaboldi, M.K. Elmore, C.E. Sheehan, B.V. Kallakury, D.W. Metzger, Delivery of IL-12 intranasally leads to reduced IL-12-mediated toxicity, Int. Immunopharmacol. 3 (2003) 801–809.
[10] T. Go, K. Nakamura, Frequent seizures with elevated interleukin-6 at the eruptive stage of exanthema subitum, Eur. J. Paediatr. Neurol. 6 (2002) 221–223.
[11] J.L. Jankowsky, P.H. Patterson, The role of cytokines and growth factors in seizures and their sequelae, Prog. Neurobiol. 63 (2001) 125–149.
[12] T. Ichiyama, M. Nishikawa, T. Yoshitomi, T. Hayashi, S. Furukawa, Tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 in cerebrospinal fluid from children with prolonged febrile seizures. Comparison with acute encephalitis/encephalopathy, Neurology 50 (1998) 407–411.
[13] J. Kawada, H. Kimura, Y. Ito, S. Hara, M. Iriyama, T. Yoshikawa, T. Morishima, Systemic cytokine responses in patients with influenza-associated encephalopathy, J. Infect. Dis. 188 (2003) 690–698.
[14] M. Kimura, M. Tasaka, H. Sejima, Y. Takusa, T. Ichiyama, S. Yamaguchi, Hemiconvulsion-hemiplegia syndrome and elevated interleukin-6: case report, J. Child. Neurol. 17 (2002) 705–707.
[15] D. Lawrence, Intranasal delivery could be used to administer drugs directly to the brain, Lancet 359 (2002) 1674.
[16] K.A. Lehtimaki, J. Peltola, E. Koskikallio, T. Keranen, J. Honkaniemi, Expression of cytokines and cytokine receptors in the rat brain after kainic acid-induced seizures, Brain Res. Mol. Brain Res. 110 (2003) 253–260.
[17] K.A. Lehtimaki, T. Keranen, H. Huhtala, M. Hurme, J. Ollikainen, J. Honkaniemi, J. Palmio, J. Peltola, Regulation of IL-6 in cerebrospinal fluid and serum compartments by seizures: the effect of seizure type and duration, J. Neuroimmunol. (2004) in press.
[18] R. Lemke, W. Hartig, S. Rossner, V. Bigl, R. Schliebs, Interleukin-6 is not expressed in activated microglia and in reactive astrocytes in response to lesion of rat basal forebrain cholinergic system as demonstrated by combined in situ hybridization and immunocytochemistry, J. Neurosci. Res. 51 (1998) 223–236.
[19] X.F. Liu, J.R. Fawcett, R.G. Thorne, T.A. DeFor, W.H. Frey, Intranasal administration of insulin-like growth factor-I bypasses the blood–brain barrier and protects against focal cerebral ischemic damage, J. Neurol. Sci. 187 (2001) 91–97.
[20] M. Minami, Y. Kuraishi, M. Satoh, Effects of kainic acid on messenger RNA levels of IL-1 beta, IL-6, TNF alpha and LIF in the rat brain, Biochem. Biophys. Res. Commun. 176 (1991) 593–598.
[21] J. Peltola, M. Hurme, A. Miettinen, T. Keranen, Elevated levels of interleukin-6 may occur in cerebrospinal fluid from patients with recent epileptic seizures, Epilepsy Res. 31 (1998) 129–133.
[22] J. Peltola, J. Palmio, L. Korhonen, J. Suhonen, A. Miettinen, M. Hurme, D. Lindholm, T. Keranen, Interleukin-6 and interleukin-1 receptor antagonist in cerebrospinal fluid from patients with recent tonic-clonic seizures, Epilepsy Res. 41 (2000) 205–211.
[23] J. Peltola, J. Laaksonen, A.M. Haapala, M. Hurme, S. Rainesalo, T. Keranen, Indicators of inflammation after recent tonic-clonic epileptic seizures correlate with plasma interleukin-6 levels, Seizure 11 (2002) 44–46.
[24] M. Penkowa, A. Molinero, J. Carrasco, J. Hidalgo, Interleukin-6 deficiency reduces the brain inflammatory response and increases oxidative stress and neurodegeneration after kainic acid-induced seizures, Neuroscience 102 (2001) 805–818.
[25] R. Racine, Modification of seizure activity by electrical stimulation: II. Motor seizure, Electroencephalogr. Clin. Neuropsysiol. 32 (1972) 281–294.
[26] S. Sallmann, E. Juttler, S. Prinz, N. Petersen, U. Knopf, T. Weiser, M. Schwaninger, Induction of interleukin-6 by depolarization of neurons, J. Neurosci. 20 (2000) 8637–8642.
[27] H. Samland, S. Huitron-Resendiz, E. Masliah, J. Criado, S.J. Henriksen, I.L. Campbell, Profound increase in sensitivity to glutamatergic- but not cholinergic agonist-induced seizures in transgenic mice with astrocyte production of IL-6, J. Neurosci. Res. 73 (2003) 176–187.
[28] A.A. Shandra, L.S. Godlevsky, R.S. Vastyanov, A.A. Oleinik, V.L. Konovalenko, E.N. Rapoport, N.N. Korobka, The role of TNF-alpha in amygdala kindled rats, Neurosci. Res. 42 (2002) 147–153.
[29] W. Sieghart, Structure and pharmacology of gamma-aminobutyric acidA receptor subtypes, Pharmacol. Rev. 47 (1995) 181–234.
[30] D.K. Song, H.W. Suh, S.O. Huh, J.S. Jung, B.M. Ihn, I.G. Choi, Y.H. Kim, Central GABAA and GABAB receptor modulation of basal and stress-induced plasma interleukin-6 levels in mice, J. Pharmacol. Exp. Ther. 287 (1998) 144–149.
[31] S.C. Steffensen, I.L. Campbell, S.J. Henriksen, Site-specific hippocampal pathophysiology due to cerebral overexpression of interleukin-6 in transgenic mice, Brain Res. 652 (1994) 149–153.
[32] A. Vezzani, D. Moneta, M. Conti, C. Richichi, T. Ravizza, A. De Luigi, M.G. De Simoni, G. Sperk, S. Andell-Jonsson, J. Lundkvist, K. Iverfeldt, T. Bartfai, Powerful anticonvulsant action of IL-1 receptor antagonist on intracerebral injection and astrocytic overexpression in mice, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 11534–11539.
[33] A. Vezzani, D. Moneta, C. Richichi, M. Aliprandi, S.J. Burrows, T. Ravizza, C. Perego, M.G. De Simoni, Functional role of inflammatory cytokines and antiinflammatory molecules in seizures and epileptogenesis, Epilepsia 43 (Suppl. 5) (2002) 30–35.

[34] Y. Yuhas, A. Weizman, S. Ashkenazi, Bidirectional concentration-dependent effects of tumor necrosis factor alpha in Shigella dysenteriae-related seizures, Infect. Immun. 71 (2003) 2288–2291.
[35] S. Zalcman, J.M. Green-Johnson, L. Murray, D.M. Nance, D. Dyck, A. Anisman, A.H. Greenberg, Cytokine-specific central monoamine alterations induced by interleukin-1, -2 and -6, Brain Res. 643 (1994) 40–49.
[36] S. Zalcman, L. Murray, D.G. Dyck, A.H. Greenberg, D.M. Nance, Interleukin-2 and -6 induce behavioral-activating effects in mice, Brain Res. 811 (1998) 111–121.
[37] S. Zalcman, I. Savina, R.A. Wise, Interleukin-6 increases sensitivity to the locomotor-stimulating effects of amphetamine in rats, Brain Res. 847 (1999) 276–283.