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Letter to the Editor

Does ketamine exert a fast-acting antidepressant effect via inhibition of pro-inflammatory cytokines?

We read with great interest the excellent article by Horacek and colleagues (Horacek *et al*. 2010), in which the authors indicated that the decrease in theta cordance could be a marker and a predictor of ketamine exerting a fast-acting antidepressant effect. We appreciate the work of their suggestive findings, which may be promising in explaining the underlying mechanism of ketamine exerting a fast-acting antidepressant effect.

Pro-inflammatory cytokines including IL-1 and TNF-α have been implicated in major depressive disorder (Hayley *et al*. 2005). Moreover, IL-1 may enhance brain serotonin transporter activity in cultured serotonergic cells and nerve terminals *in vitro*, resulting in the reduction of serotonin levels in the synaptic cleft (Zhu *et al*. 2010).

The therapeutic effect exerted by conventional antidepressants is mainly due to an increase in the level of monoamine transmitters via inhibition of serotonin and/or norepinephrine transporters located in presynaptic membranes. Unfortunately, these drugs exhibit an antidepressant effect at least 2–4 weeks after administration. Thus, there is a compelling conclusion that the therapeutic lag is a great limitation for conventional antidepressants.

Ketamine, a *N*-methyl-D-aspartic acid (NMDA) receptor antagonist, is often used for anaesthesia. Recent literature (Li *et al*. 2010) has demonstrated that ketamine exerts a robust and fast-acting antidepressant effect within 2 h after administration. However, the mechanism underlying the rapid-onset antidepressant effect of ketamine is incompletely understood. On the other hand, ketamine has been recommended for patients with sepsis because it may inhibit the endotoxin-induced pro-inflammatory cytokines including IL-1 and TNF-α both *in vitro* and *in vivo* (Taniguchi & Yamamoto, 2005). The coincidence of the fast-acting antidepressant and anti-inflammatory effects of ketamine suggests that one possible mechanism underlying the fast-acting antidepressant effect of ketamine can be attributed to its inhibition of pro-inflammatory cytokines. Further research is required to understand the perspective and discover the underlying mechanism.

Declaration of Interest

None.

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JIAN JUN YANG, ZHI QIANG ZHOU, CHUN YANG
Department of Anesthesiology, Jinling Hospital, School of Medicine, Nanjing University, China

Author for correspondence:
Dr C Yang,
Department of Anesthesiology, Jinling Hospital,
School of Medicine, Nanjing University,
305 East Zhongshan Road, Nanjing, China.
(Email: yangchuntz@sina.com)

The authors reply

The influence of a subanaesthetic dose of ketamine on circulating pro-inflammatory cytokines and serotonin in brain

In response to our article (Horacek *et al*. 2010) Dr Yang and colleagues have offered an alternative explanation for the fast antidepressant effect of ketamine. Dr Yang's interpretation suggests an inhibitory effect of ketamine on pro-inflammatory cytokines (IL-1 and TNF-α) which are upregulated in depression (Yang *et al*. 2011). Owing the fact that IL-1 and TNF-α also enhance the serotonin (5-HT) transporter, the anti-inflammatory effect of ketamine would be involved in

Table 1. *The effect of ketamine on IL-1B, TNF-α and serotonin activity*

	Ketamine ($n=11$)			Controls ($n=9$)		
	Baseline	60 min	Difference in %	Baseline	60 min	Difference in %
IL-1B (pg/ml)	889.8 (486.1)	837.8 (622.8)	92.03 (65.73)	1283 (1159)	1466 (945.3)	150.6 (91.83)
TNF-α (pg/ml)	2507 (899.5)	2357 (999.5)	92.05 (40.84)	2779 (1506)	3281 (1012)	140.1 (76.35)
	5-HT activity (brain) after ketamine			5-HT activity (brain) after saline		
	5-HT (ng/g)	5-HIIA (ng/g)	5-HIA/5-HT	5-HT (ng/g)	5-HIIA (ng/g)	5-HIA/5-HT
Frontal cortex	28.71 (3.60)	18.12 (5.34)	5.878 (2.15)	30.85 (4.60)	15.32 (4.93)	4.391 (1.43)
Hippocampus	**28.36 (4.80)***	12.69 (5.16)	4.338 (2.32)	**35.18 (7.87)***	14.25 (3.11)	3.628 (1.47)

* $p \leqslant 0.05$.

its antidepressant activity. To evaluate this hypothesis, we studied the influence of ketamine in male Wistar/Hann rats (weight 200–220 g, $n=23$) on both pro-inflammatory cytokines (IL-1 and TNF-α) and 5-HT activity in the brain.

Blood samples (1 ml) for baseline cytokine levels were obtained 24 h before the experiment from the jugular vein prepared under isoflurane anaesthesia (0.5–2%), delivered with a simple anaesthesia mask. After removing the cannula the bleeding was prevented by 30-s compression of the jugular vein followed by suturation of the skin. Twenty-four hours later we applied intraperitoneally a subanaesthetic dose of ketamine hydrochloride (Narketan, Chassot, 30 mg/kg), dissolved in 2 ml/kg b.w. of 0.9% NaCl or the same volume of saline in control animals. The effect of ketamine was evaluated 60 min later, when the rats were decapitated under short isoflurane anaesthesia. Blood was collected and brain tissue (prefrontal cortex and hippocampus) were rapidly dissected and stored at $-80\,^{\circ}$C until neurochemical analysis. All blood samples were stored at 4 °C for 1 h; after clotting they were centrifuged for 10 min at 2800 *g*. The sera were stored at $-80\,^{\circ}$C until cytokine assay. Both forms of IL-1 (IL-1A and IL-1B) and TNF-α were evaluated in 50 μl undiluted rat sera using the Bioplex 200 System and Rat Cytokine 9-Plex A Panel (Bio-Rad, USA) according to the unmodified manufacturer's instructions.

Serotonin (5-HT), its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and 5-HT turnover (5-HTIAA/5-HT) were measured in the frontal cortex and the hippocampus by LC-ESI-MS-MS analysis, described in detail elsewhere (Najmanova *et al*. 2011). The whole sample consisted of 23 animals, three animals were excluded form the analyses (two died and one had a post-operative local inflammatory reaction). The levels of IL-1A were below the detection limits (4.01 pg/ml) in all samples. The results for IL-1B, TNF-α, 5-HT, 5-HTIAA and 5-HTIAA/5-HT are displayed in Table 1 as mean (S.D.).

Both cytokines increased up to 140% and 150% only in control animals, not in the ketamine group. This finding supports Dr Yang's assumption that ketamine would prevent the pro-inflammatory cytokine activation that resulted in our experiment probably due to the preceding laboratory procedures (vein preparation, i.p. injection, etc.). However, the repeated-measures ANOVA did not confirm the effect of treatment and time for either IL-1B [$F(1,17)=1.4$, $p=$n.s.; $F(1,17)=0.18$, $p=$n.s.] or TNF-α [$F(1,19)=2.25$, $p=$n.s; $F(1,19)=0.03$, $p=$n.s.].

Ketamine administration was followed by lower 5-HT levels in the hippocampus compared to controls ($t=2.218$, $p\leqslant 0.05$). The other differences between ketamine and control conditions in 5-HT activity were not significant.

Interestingly, we found that the hippocampal 5-HT levels correlate negatively with the basal TNF-α ($r=-0.51$, $p\leqslant 0.05$) and positively with the absolute (ng/ml) and relative (%) change of this cytokine ($r=0.7$, $p\leqslant 0.05$; $r=0.7$, $p\leqslant 0.001$) in the whole sample. Similar significant findings were also confirmed for the ketamine group. This observation supports Dr Yang's assumption that TNF-α suppresses 5-HT level, and its inhibition by ketamine facilitates 5-HT. However, we did not detect any correlation between 5-HTIAA levels and TNF-α and therefore our data do not correspond with the inhibition of 5-HT transporter mediating the influence of TNF-α on 5-HT in the brain. An alternative explanation for the interaction between TNF-α and 5-HT is the inhibitory effect of pro-inflammatory cytokines on the availability of tryptophan due to increased activity of the

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enzyme indoleamine 2,3-dioxygenase (Myint *et al*. 2009).

In conclusion, our preliminary results correspond with Dr Yang's hypothesis in the following points: (*a*) the anti-inflammatory effect of a subanaesthetic dose of ketamine, (*b*) the facilitation of 5-HT in the hippocampus by ketamine, and (*c*) in the relationship (correlation) between 5-HT and TNF-α. Further experiments would elucidate the mechanisms responsible for the interaction between the inflammatory pathway and 5-HT and their relationship to the still enigmatic fast antidepressant effect of ketamine.

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Declaration of Interest

None.

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JIRI HORACEK[1], HANA TEJKALOVA[1], TOMAS NOVAK[1], VERA BUBENIKOVA-VALESOVA[1], TOMAS PALENICEK[1], LUKAS RAMBOUSEK[1], SARKA RUZICKOVA[2], SIMON VACULIN[3], CYRIL HÖSCHL[1]

[1] *Prague Psychiatric Centre, Prague, Czech Republic*
[2] *Institute of Biotechnology AS CR, Videnska, Prague, Czech Republic*
[3] *Department of Normal Pathological and Clinical Physiology, 3rd Faculty of Medicine, Charles University, Prague, Czech Republic*

Author for correspondence:
Dr J. Horacek,
Prague Psychiatric Centre, Ustavni 91, 181 03 Prague 8, Czech Republic.
(Email: horacek@pcp.lf3.cuni.cz)