



## LETTER TO THE EDITOR

# Guanosine and its modulatory effects on the glutamatergic system

To the Editor,

We read with great interest the elegant manuscript by [Deutsch et al. 2008](#) showing that guanosine is capable of reducing the ability of MK-801 (a non-competitive NMDA receptor antagonist) to raise the threshold voltage for electrically-precipitated tonic hindlimb extension in unstressed mice. The authors argue that this modulatory effect may be due to guanosine's removal of glutamate from the synaptic cleft by astrocytes, resulting in a reduced proportion of NMDA receptor-associated ion channels in the open configuration. The authors also emphasize that MK-801 is an "open-channel blocker" and its pharmacological effects are closely dependent on its entering the open channel and binding to a specific hydrophobic domain ([Deutsch et al., 2001](#)). However, we propose here a supplementary explanation for their results ([Deutsch et al., 2008](#)) and similar previous findings ([Tort et al., 2004](#)).

Non-competitive NMDA receptor antagonists such as MK-801, phencyclidine (PCP) and ketamine produce several behavioral effects in rodents, such as hyperlocomotion, stereotyped movements, ataxia, and amnesia ([Dall'Igna et al., 2003](#)). In humans, the effects of NMDA antagonists closely resemble that observed in schizophrenic patients, making NMDA receptor antagonism one of the best pharmacological models for this disorder ([Tort et al., 2004](#)). Although Deutsch and coauthors point out that the primary site of action of MK-801 is the NMDA receptor in an "open-channel configuration", the indirect contribution of other receptors, neurotransmitters and neuromodulators to the expression of its behaviors could not be fully ruled out. This might be especially important when interpreting guanosine effects on MK-801-induced behavioral disturbances.

Recent evidence suggest that NMDA receptor antagonism is also associated with glutamatergic activation of non-NMDA glutamatergic receptors induced by increased glutamate release, which appears to be closely related to the behavioral alterations observed ([Moghaddam et al., 1997](#)). Moghaddam and coworkers have further characterized the neurochemical and behavioral effects of non-competitive NMDA antagonists, demonstrating that these compounds induce an increase in the efflux of glutamate in prefrontal

cortex and nucleus accumbens ([Moghaddam et al., 1997](#); [Takahata and Moghaddam, 2003](#)). Therefore, despite of reducing glutamatergic effects at NMDA receptors, MK-801 may stimulate non-NMDA receptors by increasing the release of glutamate. These effects could be related to MK-801-induced blockade of GABAergic or other inhibitory inputs to glutamatergic neurons, strengthening the glutamatergic neurotransmission ([Takahata and Moghaddam, 2003](#)). Moreover, non-NMDA antagonists and inhibitors of glutamate release such as lamotrigine and riluzole have been shown to counteract the behavioral and neurochemical effects of non-competitive NMDA receptor antagonists ([Anand et al., 2000](#)). Although speculative, it is thus possible that such an indirect non-NMDA stimulation effect might also be underlying the MK-801 action on the paradigm employed by Deutsch et al.

In the past few years, several *in vitro* and *in vivo* antiglutamatergic effects of guanosine and other guanine-based purines have been extensively demonstrated, as recently reviewed in detail elsewhere ([Schmidt et al., 2007](#)). Briefly, we and others have shown that guanosine may be a neuroprotective endogenous compound released under excitotoxic conditions, since it protected brain slices exposed to hypoxia/hypoglycemia ([Frizzo et al., 2002](#)), prevented NMDA-induced toxicity in neurons ([Caciagli et al., 2000](#)), and induced trophic effects on neural cells ([Rathbone et al., 1999](#)). Additionally, we have demonstrated that guanosine is anticonvulsant against glutamatergic agents and amnesic at the inhibitory avoidance task in rodents ([Schmidt et al., 2000; 2005](#); [Roesler et al., 2000](#)). Regarding the mechanism of action of guanosine, a direct antagonism of glutamatergic effects is unlikely, since guanosine is a poor displacer of glutamatergic ligands ([Souza and Ramirez, 1991](#)). However, as stated by Deutsch and coauthors, guanosine has been shown to promote, mainly in excitotoxic conditions, astrocytic uptake of glutamate, which is known to play a major role in maintaining extracellular glutamate concentration below neurotoxic levels ([Schmidt et al., 2007](#)). Guanosine's effects are probably related to its interaction with specific binding sites on brain cell membranes, as previously demonstrated ([Traversa et al., 2002; 2003](#)).

Since NMDA receptor antagonists induce several locomotor effects caused at least partially by a paradoxical increase in glutamate release (Adams and Moghaddam, 2001) and given guanosine effects on the glutamate uptake by astrocytes, we recently investigated the effects of guanosine on hyperlocomotion induced by MK-801 in mice (a pharmacological model of schizophrenia). We showed that guanosine produces a ~60% attenuation of hyperlocomotion induced by MK-801, whereas it does not affect the hyperlocomotion induced by the indirect dopamine agonist amphetamine or by the non-selective adenosine-receptor antagonist caffeine (Tort et al., 2004). Of note, we have recently observed that guanosine is also able to prevent a paradoxical hypernociceptive effect induced by systemic high-dose MK-801 in rats as evidenced by the tail-flick test [unpublished data].

Considering Deutsch's and our results together, we hypothesize that MK-801 induces behavior disturbances due to a paradoxical release of glutamate and further stimulation of non-NMDA glutamate receptors. The attenuation of some behavioral effects of MK-801 by guanosine may be related to an increase of glutamate uptake by astrocytes promoted by guanosine's action at its specific binding site in cell membrane, reducing glutamate levels at the synaptic cleft and leading to less activation of non-NMDA receptors. Further experiments are currently being carried out in our laboratory to investigate this "hyperglutamatergic" hypothesis of NMDA receptor antagonists' action and its reversion by guanosine. These experiments are mainly investigating if neurotransmitter levels are indeed affected by administration of MK-801 and guanosine.

Although the mechanism of action of guanosine and its modulatory effects on MK-801-induced behavioral disturbances are not completely elucidated, these findings point to a potential antipsychotic property of guanosine. This may be especially important in targeting psychotic symptoms that are not generally treated with currently available antipsychotics. Moreover, the neuroprotective and neurotrophic effects of guanosine may also be advantageous for the treatment of schizophrenia and other brain diseases.

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## Conflict of interest

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