Comment on: Chlorpheniramine exerts anxiolytic-like effects and activates prefrontal 5-HT systems in mice (Miyata S. et al., Psychopharmacology, 2009)

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Dear Editor,

I read with great interest the recently published article by Miyata et al. (2009) in *Psychopharmacology*, regarding the connection between the anxiolytic-like effect of chlorpheniramine (CPA) and the facilitation of serotonergic neurotransmission in the prefrontal cortex (PFC). Based on their results, Miyata et al. concluded that CPA has an anxiolytic-like effect in mice that is mediated, at least in part, by facilitation of serotonergic neurotransmission in the PFC, leaving, however, open the question of where is the exact site of action of CPA in the serotonergic system.

I believe that the authors of the above-mentioned article would have found some answers to the questions raised by their research if they had referred to a relatively recent publication of our laboratory team, regarding the effects of CPA on the brain serotonergic system of the rat (Karamanakos et al. 2004). According to the results of our paper, it was demonstrated for the first time that CPA acts as an agonist at the postsynaptic 5-HT_{1A} receptors, producing hyperlocomotion and hypothermia in rats. Pretreatment with the 5-HT_{1A} receptor agonist 8-hydroxy-*N,N*-dipropyl-2-aminotetralin (8-OH-DPAT) or with the 5-HT_{1A/B} receptor antagonist pindolol enhanced or blocked respectively these effects of CPA.

In view of our experimental results, it seems that the effects of CPA on the brain serotonergic system of the mice, as presented by Miyata et al., could be possibly attributed to the stimulation of 5-HT_{1A} receptors. However, contrary to our results, Miyata et al. did not find any effect of CPA on the locomotor activity of the mice. In my opinion, this discrepancy derives from the fact that comparing to the high dose of CPA

we administered to rats (40 mg/kg, i.p.), which was enough to stimulate postsynaptic 5-HT_{1A} receptors, Miyata et al. used low doses of CPA (0.05–5 mg/kg, i.p.), which probably stimulated presynaptic and not postsynaptic 5-HT_{1A} receptors, the activation of which increases locomotor activity (Kalkman 1995). In support of this interpretation, Ahlenius et al. (1997) showed a dose-related biphasic pattern of effects of 8-OH-DPAT on endurance performance of rats on a treadmill, with enhanced performance at a low dose and impaired performance at a high dose, attributed to stimulation of pre- and postsynaptic 5-HT_{1A} receptors, respectively.

In conclusion, I suggest that Miyata et al. should have taken into consideration the results of our study, while explaining their own results, in order to strengthen their conclusions, giving at the same time a more accurate mechanistic explanation of the actions of CPA on the serotonergic system of the mice.

Yours sincerely

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