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

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Received: 23 October 2009 / Accepted: 18 December 2009 / Published online: 20 February 2010
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Dear Sir,

We are grateful to Professor Karamanakos for his suggestions about our interpretation of the anxiolytic-like effect of chlorpheniramine (CPA).

Karamanakos et al. suggested that high dose of CPA produces hyperlocomotion and hypothermia through the activation of 5-HT_{1A} receptors in the rat (Karamanakos et al. 2004). Moreover, 5-HT_{1A} receptor agonist and antagonist enhanced or blocked, respectively, the effect of CPA. Based on these results, they suggested that CPA produces its effect though the activation of the postsynaptic 5-HT_{1A} receptors.

According to his interpretation, the low dose of CPA could bind to presynaptic 5-HT_{1A} receptors and produce anxiolytic-like effects in mice because higher dose of CPA binds to postsynaptic 5-HT_{1A} receptors (Karamanakos et al. 2004). Since 5-HT_{1A} receptors are coupled with Gi/o proteins (Blier et al. 1993), the activation of presynaptic 5-HT_{1A} receptors produces the reduction of neurotransmitter release from nerve endings (Guilloux et al. 2006). We reported that local application of CPA into prefrontal cortex increases the release of cortical 5-HT which suggests that the activation of 5-HT_{1A} receptors was not involved in the effect of CPA, at least in our study. Furthermore, we could not find any reports indicating the affinity of chlorpheniramine for the 5-HT_{1A} receptor in vitro.

At this time, it is difficult to conclude that the effect of CPA is mediated by the activation of 5-HT_{1A} receptors,

especially as CPA has been reported to bind to 5-HT_{2C} receptors (Sanders-Bush and Breeding 1988). However, we acknowledge the need to perform a receptor binding study to clarify whether CPA has any binding affinity to 5-HT_{1A} receptors.

Sincerely yours,
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