Orexinergic Neurotransmission in Temperature Responses to Amphetamines

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Derivatives of amphetamines are widely abused all over the world. After long-term use cognitive, neurophysiological, and neuroanatomical deficits have been reported. Neurophysiological deficits are enhanced by hyperthermia, which itself is major mortality factor in drug abusers. Temperature responses to injections of methamphetamine are multiphasic and include both hypothermic and hyperthermic phases, which are highly dependent on ambient temperature and previous exposure to the drug. Also, amphetamine derivatives differentially affect various neuromediator systems, such as dopaminergic, noradrenergic and serotonergic.

Temperature responses to methamphetamine (Meth) at room temperature have non-trivial dose-dependence, which is far from being understood. Intermediate doses of Meth cause less hyperthermia than both low and high doses of the drug. Also, maxima of all responses have different latency responses to low and high doses are virtually immediate, while a response to an intermediate dose appears to be delayed. In our previous modeling study we demonstrated that such dose-dependence could be explained by interaction of inhibitory and excitatory drives induced by Meth [1]. Recently, we have published data on the involvement of orexinergic neurotransmission in Meth-induced temperature responses [2] where the low dose (10 mg/kg, i.p.) of SB-334867 (SB), an antagonist of the first type of orexin receptors (ORX1), was injected 30 min prior to various doses of Meth. While this dose of antagonist clearly suppressed the response to low (1 mg/kg) and intermediate (5 mg/kg) doses of Meth, the effect was statistically significant only at the late phase ($t > 60$ min) of the response to intermediate dose. At the early phase ($t < 60$ min) any drug-related changes were marred by stress-induced temperature fluctuations resulting from two intraperitoneal injections. In a separate set of experiments a high dose of the same antagonist (30 mg/kg, i.p.) suppressed the effect of low doses of Meth even more, but in contrast, it significantly amplified the responses to the higher doses (5 and 10 mg/kg) of Meth.

Understanding the mechanism that differentially affect excitatory and inhibitory components of temperature responses can have profound importance for explaining cases of life-threatening hyperthermia after Meth administration. Therefore, we performed a mathematical modeling study to provide mechanistic interpretation of SB action. Our previous model [1] was created to describe Meth-sensitive compartments and dynamics of the neural populations defining temperature responses for various doses of Meth. We hypothesized that a specific distribution of orexin receptors over the structures involved in the neural control of temperature is responsible for the complex dependence of the Meth-induced responses on the dose of orexin antagonist. To test this hypothesis we extended the model by incorporating ORX receptors that mediated Meth- and stress-dependent inputs. We showed that the low dose of antagonist almost fully suppresses the responses to both stress and intermediate doses of Meth by disruption of the corresponding inputs to the control structures. This allows hypothesizing that the excitatory component in temperature response to both stress and low dose of Meth is mediated by ORX1 receptors. Amplification of the response to the high dose of Meth at high dose of the antagonist points out to the involvement of a mechanism different from ORX1 receptor blockade. We speculate that at high doses SB becomes non-specific to ORX1 receptors and starts affecting ORX2 receptors. Further, ORX2 activation disinhibits the structure activated by high doses of Meth, which underlies the exaggerated responses to high doses of Meth at the presence of a high dose of SB. We conclude that both excitatory and inhibitory components in temperature responses to Meth administration and stress are mediated by orexinergic pathways. Non-specificity of SB at high doses to ORX1 receptors manifests itself in additional suppression of inhibition resulting in facilitation of the responses to high-doses of Meth.

Acknowledgements
This study was supported by NIH grant DA026867; iM2CS-GEIRE; IUPUI RSFG.

References

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