Nicotinic receptor-induced hypothermia: a pharmacological evaluation

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Nicotine administration to mice induces hypothermia (Zarrindast et al., 2001, Pharmacol Biochem Behav; 68: 283-289). However, the pharmacological mechanisms of this effect remain unclear and the receptor subtype(s) involved in this effect need to be elucidated. In the present studies we have assessed the role of the α_7 and $\alpha_4\beta_2$ nicotinic receptor subtypes in the hypothermic response to nicotinic agonists.

The nicotinic receptor agonists nicotine (0.375-2.5 mg/kg (free base)) (nonselective), AR-R-17779 (3-30 mg/kg) and GTS-21 (3-10 mg/kg) (α_7), epibatidine (0.001-0.003 mg/kg) ($\alpha_4\beta_2$, $\alpha_3\beta_4$), UB-165 (0.01-0.3 mg/kg) ($\alpha_4\beta_2$, $\alpha_3\beta_2$) or 5-IA (0.003-0.1 mg/kg) ($\alpha_4\beta_2$, $\alpha_6\beta_2$) were administered ip and rectal temperature measured 15 min later. In separate antagonist studies mecamylamine (0.03-3 mg/kg) (nonselective), MLA (1-10 mg/kg) (α_7), DHβE (0.3-3 mg/kg) ($\alpha_4\beta_2$, $\alpha_3\beta_2$) were administered ip 30 min prior to the agonists.

Nicotine-induced hypothermia (1.5 mg/kg ip free base) was antagonized by mecamylamine and DHβE but not by MLA. Moreover, GTS-21 and AR-R-17779 (α_7 agonists) had no hypothermic effect. In contrast, epibatidine ($\alpha_4\beta_2$, $\alpha_3\beta_4$), UB-165 ($\alpha_4\beta_2$, $\alpha_3\beta_2$) and 5-IA ($\alpha_4\beta_2$, $\alpha_6\beta_2$) induced hypothermia by -4.0, -3.65, -5.2 deg C, respectively. Epibatidine (0.002 mg/kg) and 5-IA (0.3 mg/kg)-induced hypothermia were antagonized by DHβE (1 mg/kg; 37.55 vs 35.75 and 37.47 vs 35.21 deg C, respectively). UB-165-induced hypothermia (-2.98 deg C) was not antagonized by DHβE (-2.7 deg C). However, mecamylamine reversed the effects of UB-165 (38.14 vs 36.03 deg C). (All results refer to $p<0.05$ from relevant control using 1-way ANOVA and post-hoc Dunnett's-test).

In conclusion, these data suggest that the α_7 nicotinic receptors are not involved in the hypothermic response to nicotine. A role for $\alpha_4\beta_2$ sites is suggested, but studies with UB-165 contradict this we cannot, therefore, exclude the role of other receptor subtypes.

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