Abstract

Nicotine elicits hypothermic responses in rodents. This effect appears to be related to nicotinic receptor desensitization because sazetidine-A, an α4β2 nicotinic receptor desensitizing agent, produces marked hypothermia and potentiates nicotine-induced hypothermia in mice. To determine the specificity of sazetidine-A induced hypothermia to β2 subunit-containing nicotinic receptors, we tested its efficacy in β2 knockout ($\beta2^{-/-}$) mice. These effects were compared with wildtype (WT) and α7 knockout ($\alpha7^{-/-}$) mice. Confirming our earlier results, sazetidine-A elicited a pronounced and long-lasting hypothermia in WT mice. In comparison, sazetidine-A induced a much attenuated and shorter hypothermic response in $\beta2^{-/-}$ mice. This indicates that the greater proportion of sazetidine-A induced hypothermia is mediated via actions on β2-containing nicotinic receptors, while a smaller component of hypothermia induced by sazetidine-A is mediated by non-β2 nicotinic receptors. Similar to WT mice, $\alpha7^{-/-}$ mice showed the full extent of the sazetidine-A effect, suggesting that the hypothermia produced by sazetidine-A did not depend on actions on α7 nicotinic receptor subtype. Three other novel nicotinic receptor desensitizing agents derived from sazetidine-A, triazetidine-O, VMY-2-95 and YL-1-127 also produced hypothermia in WT and $\alpha7^{-/-}$ mice. Furthermore, unlike sazetidine-A, triazetidine-O and YL-1-127 did not show any hint of a hypothermic effect in $\beta2^{-/-}$ mice. VMY-2-95 like sazetidine-A did show a residual hypothermic effect in the $\beta2^{-/-}$ mice. These studies show that the hypothermic effects of sazetidine-A and the related compound VMY-2-95 are mainly mediated by nicotinic receptors containing β2 subunit, but that a small component of the effect is apparently mediated by non-β2 containing receptors.