Effect of adenosine A_{2A} receptor ligands on voluntary ethanol intake in msP rats and on binge eating in female rats

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Adenosine A_{2A} receptors (A_{2A}ARs) are largely co-expressed with dopamine D2 receptors (D2DRs) in the central nervous system. Stimulation of A_{2A}ARs elicits opposite effects to D2DR activation at the level of second messengers and early-gene expression.

Since dopaminergic neurotransmission may have an important role in the reinforcing properties of ethanol, the present study investigated the effect of the A_{2A}AR agonists, CGS 21680 (a classical reference compound for A_{2A}ARs) and VT 7 (a more recently developed A_{2A}AR agonist that shows similar affinity for this receptor, but lacks the acidic function present in CGS 21680 [1]) and an A_{2A}AR antagonist, ANR 94 [2] on voluntary 10% alcohol intake in genetically selected Marchigian Sardinian alcohol-preferring (msP) rats. Ethanol was offered 2 h/day at the beginning of the dark phase of the cycle and drugs were administered by intraperitoneal injection, 30 min before access to it.

The acute administration of CGS 21680 or VT 7, at doses of 0.1 or 0.3 mg/kg, induced a dose-dependent reduction in alcohol intake, whereas ANR 94, 5 but not 1 mg/kg, induced a significant increase in ethanol intake, that was evident also during a subchronic treatment.

When the A_{2A}AR antagonist ANR 94, 1 mg/kg, was administered 5 min before CGS 21680, 0.1 mg/kg, the attenuation of ethanol intake induced by CGS 21680 was completely abolished.

These results indicate that A_{2A}AR agonists induce a pronounced reduction of ethanol intake in msP rats and the effect of CGS 21680 is completely abolished by an A_{2A}AR antagonist, providing evidence that it is completely mediated by this receptor subtype. These findings suggest that A_{2A}AR may represent an interesting target for the pharmacological treatment of alcoholism.

The present data raising the question of whether A_{2A}AR agonists may also control the addictive-like behaviour observed in a binge eating (BE) episode. Therefore, this study examined the effect of the two A_{2A}AR agonists: CGS 21680 and VT 7 in an experimental model of BE of highly palatable food (HPF) induced in female rats by three 8-day cycles of food restriction/re-feeding followed by acute stress.

Two groups of rats were used: NR+NS normally fed and not stressed; R+S exposed to cycles of food restriction/re-feeding and then stressed. R+S exhibited BE of HPF in amounts significantly larger than NR+NS.

The two A_{2A}AR agonists were tested at intraperitoneal doses of 0.1 and 0.05 mg/kg. Injection of 0.1 mg/kg of both agonists markedly reduced BE in R+S. However, HPF intake was significantly reduced also in NR+NS. The dose of 0.05 mg/kg was inactive. CGS 21680 and VT 7, 0.1 mg/kg, reduced also normal food pellets intake in 24 h food-deprived rats; however, they did not reduce water intake, suggesting that their effect on food intake is selective. Again, the dose of 0.05 mg/kg was inactive.

Taken together these findings indicate that A_{2A}AR agonists exert a rather general effect on food intake, inhibiting both reward based intake of HPF in sated rats and the intake of food pellets driven by homeostatic needs following food deprivation. A_{2A}AR agonists may represent pharmacological agents to control bingeing-related eating disorders, as well as to reduce food over-consumption associated with obesity.

[1] Volpini et al., 2004 ARKIVOC 5:301–311

[2] Cristalli G. et al. 2008 Current Pharmaceutical Design 14:1525-1552