Allosteric modulation of A_1 adenosine receptors as a novel and promising therapeutic strategy for anxiety

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Activation of A1 adenosine receptors (ARs) has been associated with anxiolytic-like effects in different behavioral tests, but development of A1AR agonists for therapeutic use has been hampered, most likely due to the presence of side effects. Since positive allosteric modulators enhance the function of receptors activated by endogenous agonist, they are expected to have a much lower side effect potential than orthosteric agonists, a low propensity for receptor desensitization and a high selectivity for a given receptor subtype (Urwyler, 2011). In this regard, positive allosteric modulation has proven to represent a valuable alternative to orthosteric agonists by acting on a distinct site and potentiating the effect of the endogenous agonist (Nickols & Conn, 2014). Recently, we have demonstrated the antinociceptive properties of the novel A1AR positive allosteric modulator 2-Amino-4-[(4-(phenyl)piperazin-1-yl)methyl]-5-(4-fluorophenyl)thiophen-3-yl)-(4-chlorophenyl)methanone (TRR469) in two models of acute pain such as writhing and formalin tests and in chronic streptozotocin-induced diabetic neuropathy (Vincenzi et al., 2014). With the aim to identify a safer approach for the treatment of anxiety, we investigated, in mice, the anxiolytic-like properties of the novel A1AR positive allosteric modulator, TRR469. Acute administration of TRR469 (0.3 – 3 mg/kg) resulted in robust anxiolytic-like effects in the elevated plus maze, the dark/light box, the open field and the marble burying tests. The magnitude of the anxiolytic action of TRR469 was comparable to that obtained with benzodiazepine diazepam (1 mg/kg). The use of the A1AR antagonist DPCPX (3 mg/kg) suggested that the effects of TRR469 were mediated by this receptor subtype. In contrast to diazepam, the novel positive allosteric modulator did not potentiate the sedative effect of ethanol (3.5 g/kg) evaluated by the loss of righting reflex. While diazepam produced motor coordination impairment in the rotarod test, this effect being enhanced by the presence of ethanol (1.5 g/kg), TRR469 did not elicit locomotor disturbances either when administered alone or in the presence of ethanol. In vitro, TRR469 was able to increase the number of A1AR recognizable by the agonist radioligand [3H]-CCPA in mouse brain regions involved in emotional processes. One of the great advantages of positive allosteric modulators is their ability to increase endogenous agonist affinity, enhancing the activation of the receptor in a more physiological way. In the present study we have shown that TRR469 was able to increase the affinity of the adenosine analogue CCPA in hippocampus, amygdala and prefrontal cortex membranes with an increment of 14, 17 or 32 fold, respectively, suggesting the capability, in vivo, to increase the affinity of endogenous adenosine. Taken together, these data provide compelling evidence to support the positive allosteric modulation of

A1ARs as a new interesting pharmacological strategy for the treatment of anxiety-related disorders.

Urwyler (2011). Pharmacol Rev. 63, 59-126.

Nickols & Conn (2014). Neurobiol Dis. 61, 55-71.

Vincenzi et al. (2014). Neuropharmacology. 81, 6-14.