Publication

Comparison of the phenotype of NK1R -/- mice with pharmacological blockade of the substance P (NK1) receptor in assays for antidepressant and anxiolytic drugs.

N.M.J. Rupniak, E.J. Carlson, J.K. Webb, T. Harrison, R.D. Porsolt, S. Roux, C. de Felipe, S.P. Hunt,
B. Oates and A. Wheeldon. Behav. Pharmacol., 12, 497-508, 2001.

http://www.ncbi.nlm.nih.gov/pubmed/?term=Behav.+Pharmacol.%2C+12%2C+497-508%2C+2001.

Abstract

The phenotype of NK1R-/- mice was compared with that of acute pharmacological blockade of the tachykinin NK1 receptor on sensorimotor function and in assays relevant to depressive illness and anxiety. The dose range for L-760735 and GR205171 that was associated with functional blockade of central NK1 receptors in the target species was established by antagonism of the behavioural effects of intracerebroventricular NK1 agonist challenge in gerbils, mice and rats. The caudal grooming and scratching response to GR73632 was absent in NK1R-/- mice, confirming that the receptor had been genetically ablated. There was no evidence of sedation or motor impairment in NK1R-/- mice or following administration of L-760735 to gerbils, even at doses in excess of those required for central NK1 receptor occupancy. In the resident-intruder and forced swim test, the behaviour of NK1R-/- mice, or animals treated acutely with L-760735 or GR205171, resembled that seen with the clinically used antidepressant drug fluoxetine. However, the effects of GR205171 were not clearly enantioselective in mice. In contrast, although NK1R-/- mice also exhibited an increase in the duration of struggle behaviour in the tail suspension test, this was not observed following pharmacological blockade with L-760735 in gerbils or GR205171 in mice, suggesting that this may reflect a developmental alteration in the knockout mouse. There was no effect of NK1 receptor blockade with L-760735 in guinea-pigs or GR205171 in rats, or deletion of the NK1 receptor in mice, on behaviour in the elevated plus-maze test for anxiolytic activity. These findings extend previous observations on the phenotype of the NK1R-/- mouse and establish a broadly similar profile following acute pharmacological blockade of the receptor. These studies also serve to underscore the limitations of currently available antagonists that are suitable for use in rat and mouse behavioural assays.