The NK1 Receptor Knockout Mouse Model of Attention Deficit Hyperactivity Disorder: Effects of d-Amphetamine on Impaired Cognitive Performance / Response Control in the 5-Choice Serial Reaction Time Task

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Behavioural and neurochemical abnormalities in mice lacking functional substance P-preferring NK1 receptors (NK1R-/−) resemble those associated with Attention Deficit Hyperactivity Disorder (ADHD). These include hyperactivity, which is prevented by d-amphetamine (d-AMP), a first-line medication for ADHD (see: Yan et al, 2009). Here, we used the 5-Choice Serial Reaction Time Task (5-CSRTT) to test whether NK1R-/− mice show impulsivity and inattentiveness, which are further key features in ADHD, and whether any such deficits are corrected by d-AMP.

Male NK1R+/+ and NK1R−/− mice (25-35g, 129/Sv X C57BL/6 crossed with an outbred MF1 strain) were food-deprived to 90% of their free-feeding weights and trained in the 5-CSRTT (Oliver et al, 2009). After animals’ performance had stabilized at the criterion for testing (4-13 weeks), the interval between the start of each trial and the light cue was increased from 5s to 7s (‘LITI’) so as to promote %premature responding (impulsivity) and %omissions (inattentiveness). Then, at weekly intervals, animals were given an i.p. injection of either: (a) saline (10 ml/kg), (b) d-AMP (0.3 mg/kg) or (c) d-AMP (1 mg/kg) 30 min before the LITI test or (d) retested with no injection (in order to distinguish differences in task acquisition/recall from any effect of the injection of saline or drug treatment (N=12/group). The sequence of these treatments was randomised and each was given only once to every mouse. This protocol was then repeated with a variable inter-trial interval (VITI; 2, 5, 10 or 15s), which minimises responding to the signal of time elapsed since the light cue. Differences in animals’ performance in the 5-CSRTT were analysed by split-plot ANOVA with post hoc parametric or non-parametric tests, as appropriate.

The baseline performance of the two genotypes did not differ, except for a small increase (+17%) in latency to collect the reward in NK1R−/− mice. In the LITI test, mutants perseverated more than wildtypes (+135%): aggravation of this behaviour by a saline injection (+48%) was prevented by d-AMP. In the VITI test, the genotype differences in perseveration and %omissions were abolished by d-AMP. The mutants also showed slightly lower %accuracy (-3%) and increased latency to correct responding (+15%) as well as greater %premature responding (+57%) than the wildtypes: these differences were not diminished by d-AMP. The findings indicate that deficits in cognitive performance/response control seen in NK1R−/− mice were manifested to different extents in the LITI and VITI tests, as was their modification by d-AMP. These results support our proposals that NK1R−/− mice are a model of ADHD and that certain symptoms of this disorder are a consequence of impaired NK1 receptor function.


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