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Alterations to neurexin-2 convey autistic-like behaviours in mice.

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Neurexins are presynaptic cell adhesion molecules that link to postsynaptic neuroligins or leucine-rich transmembrane repeats (LRRTMs) (1). Converging evidence suggests that neurexins support synaptic function as opposed to neural patterning (1). Recent findings from genome-wide association studies have highlighted deletions and mutations within neurexin-2 from autism spectrum disorder (ASD) sufferers (2). Little is understood about the role of neurexin-2 in vivo, especially in terms of aberrations of its function. Thus we examined neurexin-2 knockouts to determine to what extent these mice may be useful preclinical models of ASD.

Methods

The generation and confirmation of depletion of neurexin-2 has been previously described (3). Adult (>p56) neurexin-2 knockout (n=18) and wild-type littermates (n=31) on a C57BL/6J background were tested in a wide ranging battery of behavioural tests. These included, in the following order: open field, elevated plus maze, forced swim, tail suspension, three chamber sociability test, emergence test, prepulse inhibition and passive avoidance test. A minimum of three days rest was provided between less invasive tests, while two weeks rest was provided for tests involving aversive stimuli. Scoring was made automatically by computer (Stoelting Any-Maze) or by the experimenter. The average weight of wild-types was 27.6 g and 26.6 g for knockouts ($p>0.05$).

Results

Knockout mice had a replicable anxiety phenotype. In the open field, knockout mice spent the majority of their time against the outer wall (thigmotaxis) (WT:1445±40 vs KO:1596±15s, $p=0.015$). In the plus maze, they spent significantly less time in the central platform (WT:100±6 vs KO:40±4s, $p<0.0001$) and the open arms (WT:5±1 vs KO:1±0.4%, $p<0.0001$), while in the emergence test, they took longer to emerge (WT:30±5 vs KO:112±26s, $p<0.0001$) and spent more time in the enclosed shelter (WT:413±32 vs KO:592±42s, $p=0.001$). There were no significant differences in cognition (the passive avoidance test) or in tests of motivation (forced swim test and tail suspension; all $p>0.05$). Of particular relevance to ASDs, knockout mice showed strong deficits in sociability with a novel conspecific (WT:141±7 vs KO:90±9s, $p=0.001$) and in social recognition when discriminating between a previously explored mouse and a second novel conspecific (second novel conspecific: WT:86±6 vs KO:55±7s, $p=0.039$).

In conclusion, neurexin-2 knockout mice replicate core symptoms of ASDs, and present a useful tool for further research into the pathophysiology of this disorder.

(1) Reichelt AC, et al. Neuropharmacology 62(3):1519-1526, 2012.

(2) Gauthier J, et al. Human genetics 130(4):563-573, 2011.
(3) Missler M, et al. Nature 423(6943):939-48, 2003.