Autistic-like behaviour in the Parvalbumin knockout mouse

P.J.M. Gregory[1], D. Wolfer[2,3], I. Drescher-Lindh[2], H. Welzl[2,3], and B. Schwaller[1]
[1]*Institute of Anatomy, University of Fribourg, Fribourg, Switzerland, pgregory@unifr.ch*
[2]*Institute of Anatomy, University of Zürich, Zürich, Switzerland, david@dpwolfer.ch*
[3]*Department of Biology, ETH, Zürich, Zürich, Switzerland*

Introduction

The EF-hand calcium-binding protein, parvalbumin (PV), is a cytosolic protein expressed in a subset of GABA-ergic interneurons of the cerebral cortex, Purkinje, stellate and basket cells of the cerebellum, fast-twitch skeletal muscle fibres and epithelial cells of the kidney distal nephron. It functions primarily as a mobile, slow acting calcium buffer and plays a principal role in intracellular calcium homeostasis. Studies on the PV knockout mouse (PV-/-) showed an outwardly normal phenotype and lifespan. However, skeletal muscle fibres showed a reduced relaxation rate and increased fatigue resistance, coupled to a ~50 % increase in mitochondrial volume [1]. This increase in mitochondria was also observed in the soma of Purkinje cells in PV-/- mice [2]. The autism spectrum disorders (ASD) are human neuro-developmental disorders, characterized primarily by impairments in social interaction / social communication and repetitive, restrictive behaviour. Autism is increasingly being seen as an impairment or imbalance of the GABA-ergic system and due to the selective expression pattern of PV, it was hypothesized that PV-deficiency would correlate with autistic-like behaviour.

Results

Male PV-/- and wildtype (WT) mice were investigated for motor coordination, locomotion, anxiety, nociception, pre-pulse inhibition (PPI), social interaction / social novelty and restrictive, repetitive behaviour. PV-/- mice were indistinguishable from WT in tests for anxiety-like behaviour and exhibited no adverse behaviour in any of the anxiety-related assays. However, even though their average speed and distance travelled in an open-field assay were no different from WT controls, they showed significantly greater micro-linearity and fewer rearing events, suggesting a stereotypic form of locomotion. They also performed less horizontal turns (and therefore reduced "escape behaviour") in a rotarod assay, despite performing equally well, if not better, than WT mice on 3 different protocols. Both male and female PV-/- showed reduced pain sensitivity in hotplate and tail-flick assays compared to WT mice. PV-/- also showed reduced startle response at higher decibel levels than WT mice and a slightly, though not significantly, reduced (PPI). In a T-maze reversal assay, PV-/- mice showed a significantly reduced ability to reverse from an acquired behaviour compared to controls, but in an adapted 3-chamber assay for social interaction and social novelty, compared to WT the PV-/- mice showed no preference for an inanimate object (empty cage) to a novel stranger mouse, or between the 1st stranger and a 2nd mouse introduced later.

Conclusion

Deficiencies in social interaction, social communication and repetitive, restrictive behaviour are the key diagnostic criteria for ASD in humans. Adapting existing mouse behavioural assays to test for these behaviours is key to modelling autistic-like behaviour in rodents. In a series of experiments to screen for such behaviour, PV-/- exhibited deficits in reversal learning (i.e. repetitive, restrictive behaviour), but not in social interaction or social novelty. In further tests to screen for symptoms associated with, though not clinically diagnostic of, ASD, the PV-/- mice exhibited motor stereotypy and significantly reduced pain sensitivity. Even though PV deficiency may not be the underlying genetic aetiology of ASD, its absence may well be manifest in some of its symptoms. This correlates well with the documented reduction in PV-positive neurons in patients with other neurological disorders involving GABA-ergic transmission (schizophrenia, bipolar disorder) [3] and other transgenic mouse models of autism [4]. The association between chromosome 15q disorders (Prader-Willi Syndrome, Angelman syndrome), GABA receptor expression and autism is also well documented.

References

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