Overexpression of Otx2 leads to spontaneous fluctuations in manic- and depressive-like behaviour

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INTRODUCTION

Previously, we demonstrated that the transcription factor Otx2 activates a genetic network including Whn1 and Gsk3 that is essential in determining the number of monoaminergic neurons generated in the brain during development and present later in adulthood (Brodski et al., 2003).

Mouse mutants overexpressing Otx2 are hyperactive, show an increase of dopaminergic neurons and a decrease of serotonergic and noradrenergic neurons. These changes are modified by alterations in the Whn1, Bmp and Gsk3-beta pathway. Based on data suggesting polymorphisms in the Otx2 gene as a potential risk factor for bipolar disorder (Sabuncu et al., 2007), we tested the hypothesis that Otx2 overexpressing animals recapitulate aspects of bipolar disorder.

Adult Otx2 mutants show alterations in monoaminergic neurons

Otx2 show more fluctuations in sucrose preference and intake.

As quantified by an increase in the coefficient of variance mutants show main fluctuations over time in (A) sucrose preference (p = 0.014, p = 0.010) and (B) sucrose intake (p = 0.029, p = 0.010). While liquid intake does not fluctuate more in Otx2 mutants (p = 0.108). There is no significant difference in liquid intake between mutants and WT during the course of the experiments (p = 0.136).

RESULTS

Otx2 mutants show increased spontaneous fluctuations in their locomotor activity, risk taking behaviour and hedonic behaviour.

Otx2 mutants are hyperactive and show more risk taking behavior.

Animals were implanted with transducers and their activity was monitored for 5 days under normal conditions. Mutants showed increased activity throughout the dark phase and also in the first two and the last hours of the light phase (p = 0.017, p = 0.001). (A) Otx2 mutants spend significantly more time in the light compartment of the light-dark box (p = 0.011) than WT controls. (B) Frequency of entries into the center (p = 0.014), (C) frequency of entries into the open field (p = 0.016) and (D) distance traveled in the center (p = 0.016) were significantly reduced in mutants (p = 0.014) (A) treatment didn’t affect coefficient of variance for distance traveled in the center (p = 0.911). (B) Treatment significantly reduced the coefficient of variance for distance traveled in the open field (p = 0.014) for both genotypes. Lithium and carbamazepine selectively reduced (B) locomotor activity (p = 0.014) for both genotypes (A) and (B) distance traveled in the center (p = 0.014) and (D) distance traveled in the open field (p = 0.014) of the open field. Coefficient of variance was significantly reduced in mutants for both genotypes activity (p = 0.014) (A) and distance traveled in the center (p = 0.014) for both genotypes. Lithium and carbamazepine selectively reduced (B) locomotor activity (p = 0.014) for both genotypes. Lithium and carbamazepine selectively reduced (B) locomotor activity (p = 0.014) for both genotypes.

SUMMARY

Otx2 mutants show increased spontaneous fluctuations in their locomotor activity, risk taking behavior and hedonic behaviour.

Otx2 mutants are hyperactive and show increased risk taking behaviour.

Olanzapine, lithium, carbamazepine and serotonin receptor agonists reverse behavioural alterations of Otx2 mutants.

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