Stress-induced aggression in mice and evidence for preventive effects of drugs with pro-neurogenetic activity

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Several lines of evidence suggest that stress, serotonin deficiency and suppressed neurogenesis may be the factors of aggression. In the present work we have used two different paradigms of stress, pharmacological treatments and mice with deficient serotonin synthesis in the brain, in order to address these issues. Tryptophanhydroxylase-2 (TPH2) null mutant mice ($Tph2^{-/-}$) are characterized by increased aggressive behaviour in baseline conditions, while naïve heterozygous mice ($Tph2^{+/-}$) lack such behavioural changes. In the present study, $Tph2^{+/-}$ male mice were subjected to a 5-day predator stress followed by the resident-Intruder test. In comparison to their wild type littermates, non-stressed $Tph2^{+/-}$ mice showed no changes in parameters of aggressive, dominant-like and social behaviours. However, stressed $Tph2^{+/-}$ mice displayed elevated measures of aggressive behaviour, such as reduced latency of the first attack and increased duration of fighting behaviour. In contrast to $Tph2^{+/-}$ mice, wild type mice subjected to predator stress showed a significant reduction in the measures of aggressive behavior, such as an increased latency of the first attack, reduced number and duration of attacks. These data suggest that predator stress evokes opposing effects on aggressive behaviour dependently on congenital Tph2 levels. HPLC measurements of monoamines revealed a strong positive correlation between aggressiveness and serotonin turnover rate in striatum in stressed wild type animals ($Tph2^{+/+}$), while in naive $Tph2^{+/-}$ mice there was a correlation between aggressiveness and serotonin turnover rate in prefrontal cortex. Therefore, it can be assumed that heterozygous animals use serotonin to process the situation of resident-intruder test through different brain areas. In another study, male Balb/c mice were subjected to a 3-week ultrasound radiation in 20-45 kHz frequencies ranges, which was recently shown to evoke emotionally negative state and affective disturbances. It was found that this challenge has induced aggressive-like changes. We have also studied a potential anti-aggressive effect of a 2-week administration of two pro-neurogenetic substances with different mechanisms of action, a new analogue of dimebon DF302 and thiamine (vitamin B1) at the doses of 40 mg/kg/day and 200 mg/kg/day respectively, in this paradigm. Both compounds were previously shown to counteract stress-induced suppression of neurogenesis. Aggressive behaviour was evaluated in the resident-Intruder test. It was found that mice subjected to a three-week ultrasound exposure, had significantly decreased latency of attacks, and significantly increased number and duration of attacks, in comparison to the control group. At the same time, mice treated with DF302 and thiamine displayed no changes in the measures of aggressive behaviour, as compared with the control non-stressed group. To sum up, first, stress of various origins can precipitate or result in the excessive aggression. Second, the substances that increase neurogenesis can prevent these negative effects of the stress on aggressive behaviour.