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Dissertations-Kurzfassung

Involvement of hippocampal neurogenesis in the development of anxiety in voluntarily exercising mice

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Several studies investigated the effect of physical exercise on emotional behaviors in rodents; resulting findings however remain controversial. In an attempt to evaluate the effect of physical exercise on emotional behaviors and brain plasticity, C57BL/6J male mice were individually housed in cages equipped with a running wheel. Three weeks after continuous voluntary running we assessed anxiety- and depression-like behaviors. Tests included Openfield, Dark-Light-Box, Elevated O-Maze, Learned Helplessness, and Forced Swim test. Corticosterone metabolite levels were measured in feces collected over a 24 h period and brain-derived neurotrophic factor (BDNF) in several brain regions. Furthermore, cell proliferation and adult hippocampal neurogenesis were assessed.

Voluntary wheel running induced increased anxiety in the Openfield, Elevated O-Maze, and Dark-Light-Box as well as higher levels of excreted corticosterone metabolites. No antidepressant effect of running was observed despite a significant increase of hippocampal neurogenesis and BDNF. Instead, numbers of differentiating neurons correlated significantly with anxiety parameters in the Openfield and Dark-Light-Box.

In a second study we investigated whether this correlation of neurogenesis and anxiety was just an epiphenomenon or was causative in inducing anxiety. Indeed, reducing neurogenesis by focalized irradiation of the hippocampus abolished the exercise-induced increase of anxiety, suggesting a direct implication of hippocampal neurogenesis in the observed phenotype. On the other hand, irradiated mice explored less frequently the lit compartment of the Dark-Light-Box test irrespective of wheel running, suggesting that irradiation *per se* induced anxiety as well. Thus, our data suggest that intermediate levels of neurogenesis are related to lowest levels of anxiety. Moreover, using c-Fos immunocytochemistry as cellular activity marker, we observed significantly different induction patterns between runners and sedentary controls when exposed to a strong anxiogenic stimulus. Again this effect was altered by irradiation. In contrast, the well-known induction of brain-derived neurotrophic factor (BDNF) by voluntary exercise was not disrupted by focal irradiation, indicating that hippocampal BDNF levels do not directly correlate with anxiety under these experimental conditions. In summary, our data demonstrate to our knowledge for the first time that increased neurogenesis can have a causative implication in the induction of anxiety.