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SPECIAL ISSUE

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Neurogenesis and depression: what animal models tell us about the link

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Abstract There is growing evidence that stress causes a decrease of neurogenesis in the dentate gyrus and antidepressant treatment in turn stimulates the cell proliferation in the dentate gyrus. This has led to the hypothesis that a decreased neurogenesis might be linked to the pathophysiology of major depression. The article reviews the relationship of depressive-like behavior and neurogenesis in three animal models of depression with high validity: learned helplessness, chronic mild stress and chronic psychosocial stress of the tree shrew. All animal models provide evidence that stress which can lead to depressive-like behavior, in parallel causes a decrease of neurogenesis; vice versa, antidepressant treatment is able to revert not only behavioral changes but also to normalize neurogenesis. But the animal models argue against the notion that decreases of neurogenesis are the cause or the consequence of depressive-like behavior since depressive-like behavior can occur without impairments in neurogenesis and decreasing neurogenesis does not neccessarily lead to depressive-like behavior. This suggests that neurogenesis does not directly control affect but is tightly connected to the modulation of affect by stress and antidepressant measures.

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Introduction

In the last 15 years, much has been learned about the mechanisms regulating and modulating the proliferation, differentiation and integration of new neurons throughout adulthood. This new knowledge has generated excitement and lively debates among scientists as well as in the interested public. The finding of adult neurogenesis opens the possibility of treating the loss of neurons from trauma or degenerative diseases with interventions stimulating the formation of new neurons. But much remains to be learned before we can use our knowledge to cure patients.

There is agreement that in the dentate gyrus of the hippocampus, stem cells retain the capacity to proliferate and differentiate into functional neuronal cells and are integrated into the existing neuronal networks within several weeks (Palmer et al. 2000; Ming and Song 2005; Gage 2002). In contrast, little is known about the impact of the newly formed cells on behavior. New neurons seem to contribute to some forms of learning and memory, for example hippocampus dependent trace conditioning and spatial learning, and possibly episodic memory as well (Aimone et al. 2006; Leuner et al. 2006). There is indirect evidence to the hypothesis that neurogenesis might also have a function in mood regulation and may be reduced during depression (Jacobs et al. 2000).

Recent reviews make the connections between neurogenesis and depression clear (Dranovsky and Hen 2006; Duman and Monteggia 2006; Fuchs et al. 2004). In brief, the argument is that stress plays a major role in depression where stress and stress hormones lead to reduced hippocampal volume and decrease the rate of neurogenesis in the dentate gyrus,

which could account for the hippocampal volume reduction which is also seen in depression. Antidepressants appear to increase the rate of neurogenesis, and protect from adverse stress effects. These data lead to the conclusion that these medications may be working through an activation of neurogenesis and to the hypothesis that decreased rates of neurogenesis might be the final common pathway leading to depression. Alternatively, neurogenesis could be an associated phenomenon which does not in fact trigger the behavioral changes leading to depression (Henn and Vollmayr 2004).

Stress models

With animal models we can address the question: is depressive-like behavior correlated with a decrease of neurogenesis and if so, which of the symptoms can be explained by a reduction of neurogenesis? Ideally, in a perfect animal model one would like to have identical causative conditions to the human disease state (= etiological validity), identical symptom profiles to those observed in the disease state (= face validity), and identical treatment responses to those seen in the human disease (= predictive validity).

Etiological validity

Most of the well established models for depression use stress to induce depressive-like states. These stress-models are particularly suitable to investigate the connection between neurogenesis and depression because the neurogenesis hypothesis is based on the fact that stress decreases neurogenesis and can elicit depression. Among the stress models, learned helplessness (LH), chronic mild stress (CMS), and psychosocial stress are best established. In the learned helplessness model, inescapable and uncontrollable stress is used to induce depressive-like learned helplessness behavior, while escapable and controllable stress has no serious consequences. The central role of controllability in the learned helplessness paradigm was observed early on and appears to be a factor in the conditions leading to human depression (Kendler et al. 2003). As in humans, the rat medial prefrontal cortex is involved in detecting controllability and the pathogenesis of learned helplessness which supports the usefulness of this paradigm as an animal model for depression (Amat et al. 2005). In the CMS-model chronic unpredictable mild stress like soiled cages, changing cage mates or unpredictable feeding times is used to induce depressive–like behavior. In this model stressors are applied over a considerable time from 3 weeks to 3 months, thus mimicking long-lasting stress leading to human depression (Willner et al. 1992). Finally, the model of chronic psychosocial stress of the tree shrew combines uncontrollability and chronicity of the stressor in a paradigm of natural relevance. Male tree shrews defend their territories against intruders. When two adult males are housed together in one cage, they will fight and establish a social hierarchy with a dominant and a subordinate male. The subordinate experiences chronic stress as long as it lives in visual and olfactory contact with the dominant male (Fuchs and Flügge 2002).

Assessment of depressive-like behavior in animals

Learned helplessness is assessed 24 h after stress in an escape test probing the animal's ability to learn an escape response. Learned helpless animals show increased escape latencies and more escape failures when compared to not-learned helpless or escapably stressed animals. Furthermore, helpless animals show a wide variety of symptoms seen in depressive illness such as anhedonia, motivational deficits, autonomous and endocrine changes in analogy to major depression. If stress of moderate intensity is used, the behavioral outcome after inescapable stress varies between individuals. Comparing helpless animals to those not developing helplessness after stress allows the separation of unspecific stress effects from those effects which are specific to behavioral changes. Animals exposed to CMS develop an anhedonic state, thought to be a hallmark of the depressive condition, which is usually assessed as decreased sensitivity to the rewarding properties of sweet solutions or by an increased threshold to brain stimulation. CMS also induces a wide variety of depressive-like vegetative and neuroendocrine symptoms. Finally, subordinate tree shrews exposed to chronic psychosocial stress develop affective behavior similar to depressed patients with decreased grooming and marking behavior. In addition, they also show neuroendocrine changes of the stress responsive systems and vegetative changes characteristic for depression such as disturbed sleeping patterns and decreased intake of food and water.

Predictive validity

Predictive validity requires a behavioral response to antidepressants that involves a time delay in onset of action and specificity only for clinically active antidepressants. In all three of the stress models, CMS, learned helplessness and chronic psychosocial stress of the tree shrew depressive-like behavioral, neuroendocrine and vegetative changes are specifically responsive to a wide variety of tested antidepressants as well as electroconvulsive treatment (Vollmayr and Henn 2003; Willner 1997; Fuchs and Flügge 2002).

Tests of depressive-like behavior

In contrast to the animal models mentioned above, depressive-like behavior in the following paradigm is spontaneous and not stress-induced. The test assesses anxiety, an affective behavior related to depressive symptoms. Santarelli et al. (2003) introduced the novelty suppressed feeding (NSF) as a test of a behavior responsive to chronic (28 days) but not subacute (5 days) antidepressant treatment. In this paradigm an animal is placed in an open field with a brightly illuminated center where food is placed and the animal must overcome its fear of the brightly lit spaces to reach the food. The latency to begin feeding has classically been used as a measure of anxiety to screen for anti-anxiety agents like benzodiazepines but, as demonstrated by Santarelli et al. (2003), also has predictive validity for antidepressant action. It is important, however, to remember that it is not an animal model in a strict sense because novelty suppressed feeding is part of the species specific behavior under normal circumstances and is not a behavior induced by a severe or chronic stressor. As depressive episodes can be elicited by stressful experiences, for the etiological validity of an animal model a stress-induced change of behavior is necessary. If the etiological validity of a test of depressive-like-behavior is limited, conclusions to the pathophysiology of the disease must be drawn with caution.

Neurogenesis in animal models

Studies in all animal models confirm the finding that stress decreases dentate gyrus cell proliferation and survival of newborn cells, whereby antidepressant measures increase neurogenesis: in all tested animal models a severe and long lasting decrease of dentate gyrus cell proliferation and neurogenesis was observed regardless of which stressor was used. Inescapable stress of the LH paradigm reduced proliferation and neurogenesis (Malberg and Duman 2003; Vollmayr et al. 2003), an effect repeated in the chronic psychosocial stress model (see Czeh and Lucassen, this issue), whereby behavioral changes as well as decreases of neurogenesis after stress were reversed by antidepressant treatment. CMS decreased the cell proliferation and the survival of new-born cells in the dentate gyrus with escitalopram treatment restoring neurogenesis only in those animals that recovered from anhedonia (Alonso et al. 2004; Lee et al. 2006; Jayatissa et al. 2006). Furthermore, Santarelli et al. (2003) demonstrated that an increase in neurogenesis was necessary for the antidepressants effect on behavior. The authors used x-ray treatment of the hippocampus to reduce neurogenesis by over 80% and showed that this disrupted the behavioral effects of fluoxetine and imipramine on novelty suppressed feeding. In the second approach, it was shown that serotonin receptor 1A (5-HT_{1A}) knockout mice were insensitive to the effects of fluoxetine on behavior or neurogenesis, however both effects on neurogenesis and behavior were seen when imipramine, which acts via the noradreneric, as well as the serotonergic system, was utilized. Both findings suggest the drugs worked through increasing neurogenesis.

At the first glance, these data seem to strongly support the hypothesis that neurogenesis is associated with depressive-like behavior, perhaps is even causative for depressive-like behavior. However, the above mentioned studies report several observations incompatible with this notion: Santarelli et al. (2003) noted that the 5-HT_{1A} knockout mice had a greater latency to feed than wild type mice but had exactly the same rate of cell proliferation. Also, irradiated mice had virtually no neurogenesis but showed normal behavior in novelty suppressed feeding and grooming score. Likewise, we found that a decrease in cell proliferation after immobilisation stress does not predict helpless behavior (Vollmayr et al. 2003) and Malberg and Duman (2003) reported that, not only did inescapable stress cause decreases of dentate gyrus cell proliferation, but also escapable stress that did not induce learned helplessness. We also noted that inescapable stress reduced the proliferation unspecificly in all stressed animals, even in those not responding helpless. Futhermore, learned helplessness was apparent 24 h after the stressor, before the cell proliferation was inhibited (Vollmayr et al. 2003). This clearly indicates that decreases of neurogenesis are not necessary for depressive-like behavior and decreased neurogenesis does not neccessarily lead to altered behavior in the tested paradigms.

In summary, animal models of depression provide evidence that neurogenesis in the dentate gyrus and cell proliferation do not correlate with depressive-like behavior per se, but rather with factors modulating this behavior such as stress and antidepressant treatment. Most likely, neurogenesis is linked to functional changes in the neural systems from brain stem to fronto-limbic regions that convey negative stress effects as well as beneficial pharmacological effects, but depression is complex and involves a complex neural system not connected to neurogenesis (Goldapple et al. 2004). One may object that neurogenesis could be causally linked to a depressive symptom not captured by the existing animal models. In particular, newborn cells in the dentate gyrus seem to participate in learning and memory (Wiskott et al. 2006; Leuner et al. 2006) and one might speculate that an impaired hippocampal function secondary to impairments in neurogenesis could be the cause of deficits in episodic memory characteristic for depressive episodes. This speculation becomes even more intriguing by a recent report suggesting that young granule cells could contribute to the encoding of time in memories (Aimone et al. 2006). New par-

adigms to assess the association of temporal memory in rodents possibly will help to understand how temporal information is stored in memory and how this process is disturbed in depression.

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