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**Department of Physiology and Pharmacology**

# Pharmacological and Genetic Modulation of Adult Neurogenesis in Animal Models Relevant to Neuropsychiatric Disorders

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## ABSTRACT

During the past decade, the modulation of adult neurogenesis has been an intensively studied area of neuroscience due to the implications for understanding of physiological mechanisms in the adult brain and the potential clinical applications for neuropsychiatric disorders. This research has resulted in countless discoveries during a relatively short period of time elucidating mechanistic details about where adult neurogenesis takes place, how the process of neurogenesis occurs and how this process can be regulated at several different steps by, not only endogenous mechanisms which normally maintain a homeostasis of adult neurogenesis, but also by exogenous regulation using genetic and pharmacological modulations to manipulate steps of the process. The modulation of adult neurogenesis has been demonstrated to notably occur as a result of chronic antidepressant treatment which affects several stages of this process resulting in increased adult neurogenesis. A consensus of studies examining the importance of this modulation agree that this increase could be an integral and important part of the behavioral effects of antidepressant, indicating that increased neurogenesis is a part of the therapeutic process in the majority of treatment methods. Questions remain though regarding how neurogenesis is involved in modulating mood as a consensus on this matter finds that decreases in adult neurogenesis *per se* do not induce depression. However, recent studies indicate that adult neurogenesis is important in the regulation of stress, suggesting that a consequence of decreases in adult neurogenesis may play a role in the dysregulation of this endocrine system in combination with severe or chronic stress which may eventually result in depression. These findings highlight the potential significance of treatments which have the potential to increase adult neurogenesis during pathological states to reach stable levels.

Current findings indicate that one of the most important and accessible systems in modulating neurogenesis is the serotonergic system, as exemplified by the potent ability of serotonin enhancing drugs such as the antidepressant fluoxetine to increase neurogenesis. A first set of studies present in this thesis investigate the neurogenic potential in the hippocampus of proteins of the S100 family associated with the serotonergic system including p11 and S100B. The first of these studies uses a genetic deletion of p11 in mice. Results from these experiments demonstrate that mice lack a neurogenic and behavioral response to fluoxetine, seen in normal mice. This finding indicates that p11 is involved in the antidepressant mechanism of fluoxetine. Further examination into potential mechanisms revealed that p11 is highly expressed in interneurons which also express low levels of 5-HT1B and 5-HT4 receptors, of which p11 is a known adaptor protein. Interneurons are known to regulate aspects of adult neurogenesis indicating a possible mechanism through which p11 may modulate the neurogenic and furthermore behavioral effects of this antidepressant. A subsequent study identifies other areas of the brain potentially involved in depression which express p11 and 5-HT1B and 5-HT4 receptors. The last of these S100 studies uses a genetic amplification of S100B in mice to investigate its potential role in adult neurogenesis and revealed that S100B mice have an increased baseline level of cell proliferation which however did not translate into an increase in total neurogenesis. Furthermore, these mice display a normal neurogenic and behavioral response to fluoxetine. These results indicate that S100B is involved in cell proliferation though not other aspects of neurogenesis. Furthermore, S100B may be partially involved in aspects of neurogenesis enhancing drugs and highlight the potential benefits of modulation of this protein.

Besides the serotonergic system, other neurotransmitter systems have been implicated in the regulation of adult neurogenesis, including the dopaminergic system. Altered dopamine levels are associated with several disorders of the brain with neuropsychiatric complications. Furthermore this system, in similarity to the serotonergic system, is a primary target of pharmacological therapies for neuropsychiatric disorders. A second set of studies therefore further investigated effects of pharmacological and genetic modulation of the dopaminergic system on adult neurogenesis. The first of these studies investigated the neurogenic and behavioral effects of the drug sarizotan which targets both the serotonergic and dopaminergic system. This drug has previously been shown to have potential antidyskinetic beneficial effects against involuntary movements seen in Parkinson's disease and therefore we investigated effects of this drug in an animal model of Parkinson's disease in which dopaminergic afferents are lesioned unilaterally. In the lesioned hemisphere, sarizotan increased cell proliferation in two neurogenic regions of the lateral ventricles and the hippocampus. Sarizotan in combination with the anti-Parkinsonian drug L-DOPA, also increased ongoing neurogenesis in the hippocampus. Furthermore, sarizotan had antidepressant-like activity in the forced swim test in lesioned animals. These findings indicate that targeting of both the serotonergic and dopaminergic systems may be an effective modulator of aspects of neurogenesis and behavior in certain pathologies. For example sarizotan may, in addition to antidyskinetic effects, have antidepressant potential in the frequently seen subgroup of Parkinson's disease patients who also suffer from depression.

The numerous studies regarding purely dopaminergic regulation of adult neurogenesis in either the lateral ventricles or hippocampus have resulted in conflicting data suggesting a complex regulation in which several receptors may be involved. Currently available data suggest expression of the D3 receptors in the proliferative zone of the hippocampus indicating a role in adult neurogenesis. The role of the D3 receptor using a genetic deletion of this receptor in mice was therefore investigated. A robust increase was found in baseline levels of cell proliferation and ongoing neurogenesis in these mice, though not in cell survival. Furthermore, pharmacological modulation using the preferential D3 antagonist S33138 had a similar effect on cell proliferation, although less robust. Thus, in the hippocampus, the D3 receptor appears to act inhibitory on cell proliferation. Previous indicating that D3 is expressed in proliferating cells indicates that this may be a direct effect of dopamine whereas expression of D3 and D2 receptors on niche astrocytes may in contrast indirectly stimulate cell proliferation. This study further highlights how modulation of the dopaminergic system affects adult neurogenesis and may ultimately have significance for pathologies in which adult neurogenesis is affected.

In summary, these findings exemplify the numerous different ways in which adult neurogenesis can be modulated which is also indicative of the situations in which adult neurogenesis can be defective, potentially contributing to disease. Studies presented in this thesis have via the use of genetic manipulation as well as pharmacological compounds highlighted specific proteins and pharmacological targets which can be used to modulate aspects of neurogenesis, having potential clinical significance for neuropsychiatric disorders in which adult neurogenesis is affected. ISBN 978-91-7457-650-4