FROM ADOLESCENT NEUROGENESIS TO SCHIZOPHRENA: OPPORTUNITIES, CHALLENGES AND PROMISING INTERVENTIONS

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ABSTRACT

Schizophrenia is a maldevelopmental disease with multifactorial etiopathogenesis linked to disturbances in the prenatal/perinatal environment and to social factors and/or addictive drugs consumption during adolescence/young adulthood. Adolescence has been demonstrated to represent a very sensitive period for brain development. Exposure to adverse life events (chronic social isolation and/or instability) and/or addictive drugs (opioids, cocaine, cannabinoids, alcohol, nicotine) during adolescence has been linked to deviations in the normal neurodevelopment, producing a brain particularly at risk of mental diseases. Several psychopharmacological drugs and environmental factors have been reported to protect against the detrimental effect on neurogenesis caused by the aforementioned genetic and/or epigenetic vulnerabilities. Nerve growth factor (NGF) is one of the strongest stimuli of adult/adolescent neurogenesis and a promising neuromodulator to prevent and/or ameliorate the various behavioral and cognitive schizophrenic symptoms. Biomed Rev 2017; 28: 62-69.

Key words: schizophrenia, neurodevelopment, adolescence, stem cells, adult neurogenesis, addictive drugs, life events, NGF

INTRODUCTION

Schizophrenia (SCZ) is considered a disease of abnormal brain development, with an elevated incidence of the disease being linked to a wide range of disturbances in the prenatal/perinatal environment and to social factors and/or addictive drugs consumption during adolescence/young adulthood (1). An appropriate proliferation, migration, differentiation, synaptogenesis, and finally pruning of new neurons represent essential steps for a healthy brain development (2). For over a century, it has been thought that the capacity of germinal layers to generate neurons was restricted to the embryonic period, and that new neurons could not be added to the adult mammalian brain: “In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be generated” (3). Besides, probably due to the impossibility to determine with certainty the neural nature of the cells presenting mitotic figures, occasional early reports of neurogenesis in the central nervous system (CNS) were completely ignored (4-5). It was not until more than fifty years later that the pioneering work of Smart et al (6) and Altman (7) demonstrated ongoing neurogenesis, as judged by incor-
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Porportion of 3H-thymidine, in some regions of the adult rodent brain. In 1998, overthrowing the dogma of a fixed neuronal complement at birth or soon after, adult neural stem/precursor cells were finally identified as a source of new neurons also in the mammalian CNS including humans (8).

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This had profound implications for adolescent-onset neurodevelopmental disorders such as SCZ. Indeed, since it is now known that neurogenesis, within specific adult brain regions including the dentate gyrus (DG) of the hippocampal formation (HF) and the ventricular zone/subventricular zone/olfactory bulb (VZ/SVZ/OB) system, continues in postnatal life well into adolescence and beyond, the characteristic age at onset of this disorder - late adolescence or early adulthood, precisely - suggests that SCZ could arise from a pathological regulation of adult/adolescent neurogenesis (9). In line with this hypothesis, abnormalities of the hippocampus, mainly a subtle but significant volume difference, as well as explicit pathological features in the hippocampus neurogenic niche, are one of the most consistent findings in SCZ research to date (10-22). Moreover, paradigms modeling hippocampal neurogenesis - using fibroblasts-derived induced pluripotent SCs (iPSCs) from patients with SCZ - have found deficits in the generation of DG granule neurons with lowered levels of key embryonic development and/or adult neurogenesis genes, reduced neuronal activity, and reduced levels of spontaneous neurotransmitter release (23). Regarding VZ/SVZ/OB’s neurogenic niche, albeit the most common neuroanatomical change in patients with SCZ is enlarged lateral ventricles (13, 24), up to date, no associations have been found between this ventricular enlargement and cytointactural alterations of VZ/SVZ in SCZ (25). In contrast, numerous imaging studies have reported olfactory sulcus depth abnormalities and OB volume reductions in patients diagnosed with SCZ (26, 27), also with a number of studies reporting various olfactory deficits (28-30). Of note, these deficits are not explained using medications, cognitive impairments, or smoking status; instead, they support the hypothesis of primary dysfunction in the olfactory system. As for hippocampus, paradigms modeling SCZ - using olfactory mucosal cultures from patients with SCZ - have in fact demonstrated significant disease-specific alterations in gene expression, protein expression, and cell function, including deregulated neurodevelopmental pathways associated with cell proliferation, adhesion, migration, and cell death (31).

Apart from the prenatal/perinatal period, adolescence has been demonstrated to represent a very sensitive period for brain development. With specific regard to cell proliferation/survival, studies have shown that adolescents have higher levels of neurogenesis in the hippocampus - an 80% loss in granule cell production from adolescence to young adulthood (32-34).

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In line with these findings, a decrease in the addiction of new cells during the adolescent period has also been reported in the prefrontal cortex (35). Exposure to adverse life events and/or addictive drugs during adolescence has been linked to deviations in the normal neurodevelopment, in a sort of continuum – starting from the prenatal/perinatal alterations – producing a brain particularly at risk of mental diseases such as SCZ (9, 36-39). Delayed maturation and/or damage to specific brain regions, such as the hippocampus and prefrontal cortex, further increase the likelihood of ongoing drugs addiction (40). Of note, these same brain regions, in particular hippocampus, are those reported to be significantly affected with regard to neurogenesis when exposed to the aforementioned adolescence SCZ socio-environmental risk factors. What is more with structural, neurochemical, cognitive, and behavioral alterations specific to the SCZ disorder that have been demonstrated in animal models of perturbed neurogenesis (41-43). Chronic social isolation and/or instability, addictive drugs such as opioids, cocaine, cannabinoids, alcohol, nicotine, and even chronic sleep restriction or fragmentation typical of the adolescent period, all have been reported to elicit acute and/or enduring negative effects on adult hippocampal neurogenesis, with the adolescence and/or the young adulthood period which have been proved to be particularly sensitive to their adverse effects (9, 44-52). Of note, as for a delayed hippocampus maturation and/or damage, a low hippocampal neurogenic activity has in turn been associated to addiction (53).

Supporting the hypothesis of a combination of different genetic and/or socio-environmentally epigenetic modifications at the base of SCZ, the exposure to the aforementioned adverse life events and/or addictive drugs has been linked to a reduced and/or altered expression/function of the most acknowledged SCZ susceptibility genes [Disrupted in schizophrenia 1 (DISC1); Neuregulin-1 (NRG-1); MicroRNA-137 (miR137)] and the different intrinsic/extrinsic factors im-
pacting on adult neurogenesis [Wnt/β-catenin; Notch signal; Neural cell adhesion molecule (NCAM); glutamate, Gamma-Aminobutyric Acid (GABA), Dopamine (DA) and their corresponding receptors; Neurotrophins (NTs)] (9). In a sort of vicious circle, DISC1, NRG-1, NCAM, GABA, DA, and specific NTs alterations (Brain Derived Neurotrophic Factor (BDNF) - Val66Met) have also been indicated as possible contributors to various forms of addiction (9), even with some studies that have demonstrated specific gene environmental stressors (adolescent social isolation/social defeat paradigms, cannabis exposure) interactions affecting brain development and functions during the critical period of adolescence (9).

NEUROPROTECTIVE FACTORS

In the light of the foregoing, a number of studies have been conducted with the purpose of evaluating the possibility to act on neurogenesis and associated SCZ behavioral/cognitive impairments. Electroconvulsive therapy, atypical antipsychotics, serotoninergic antidepressants as well as agomelatine, lithium, valproate, moderate physical activity and/or environmental enrichment have all been reported to exert a positive effect on neurogenesis, in some cases demonstrating the capacity to protect against the detrimental effect on neurogenesis caused by the aforementioned genetic and/or epigenetic vulnerabilities (43, 54-61). Recent reviews and various research findings have suggested that glycogen synthase kinase-3beta (GSK-3β) phosphorylation/inactivation may be central in their mechanisms of action (62-65). Of note, this same molecule represents one of the interacting and/or associated protein of DISC1 gene and even of key signaling controlling adult neurogenesis such as Wnt/β-catenin and Reelin (9). Through the inhibition of GSK-3β (or histone deacetylase) via multiple signaling cascades such as the PI3K/Akt and the MAP kinase (MEK)/ERK pathways, all these treatments have been hypothesised to regulate the transcription/expression of different neurotrophic, angiogenic, and neuroprotective proteins (59). Both PI3K/Akt and MEK/ERK pathways have, as a downstream target, the cyclic adenosine monophosphate response element transcription factor (CREB). This latter, when activated through phosphorylation, modulates the expression of neurotrophic and cell-protective proteins, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and Bcl-2 (9, 65-67). Noteworthy, BDNF and NGF have been reported to function as both downstream molecules resulting from the inhibition of GSK-3β and upstream signals able to inhibit this molecular pathway (9, 65, 68).

NGF AS STIMULUS OF ADULT/preadOLESCENT NEUROGENESIS

With specific regard to NGF, different research findings suggest its role in continued neurogenesis and neuroplasticity as well as in the development of various neurological and psychiatric disorders characterized by neurocognitive dysfunction including SCZ (69-71). Increased survival of SVZ and/or the hippocampus DG progenitor cells has been observed following the induction of brain NGF synthesis in particular psychosocial stress mouse models (72,73), because of voluntary moderate physical exercise (74), environmental en-richment (75,76), and/or various pharmacological treatments (76). Intracerebrally injected, NGF also promotes the differentiation of SVZ neuronal precursor cells in aged mice (77) and in animal models of neuroinflammatory brain diseases (78, 79), thus indicating how the administration of exogenous NGF can actually mimic the effect of the endogenous form on the immature neuronal cells. Of note, NGF has been proved to exert its biological actions also when applied as eye drops (oNGF) or intranasal (80-83). Early studies in an animal model of diabetes-streptozotocin (STZ) induced cell death demonstrated that oNGF was able to counteract the alteration of mature/pro-NGF expression in the SVZ, affecting the survival and differentiation of SVZ progenitors, further neutralizing the reduction in the number of neuroblast type A cells and the number and distribution of C-type cells and type B cells (84-86). In a subsequent study, these latter authors reported how oNGF was able to modulate BDNF signaling in the prefrontal cortex of healthy rats and might influence the manifestation of depressive phenotype in diabetic rats (87). In line with these findings, intranasal NGF administration has been reported to rescue neurogenesis and/or neurological impairments in animal models of Alzheimer’s disease, ischemia as well in patients with severe brain injuries (81-83).

Taken together, these results suggest NGF as one of the strongest stimuli of adult/adolescent neurogenesis, further suggesting the DG of the HF and the VZ/SVZ/OB system as possible targets for this talented molecule in preventing and/or ameliorating the various behavioral and cognitive SCZ symptoms (88).

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