

Alterations in Postnatal Neurogenesis And Dopamine Dysregulation in Schizophrenia: A Hypothesis

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An increasing number of studies demonstrate the important role of several susceptibility genes for schizophrenia, such as *neuregulin-1* and *DISC1*, in early postnatal and adult neurogenesis. Its significance for the pathophysiology of the disease, including its relation to neurotransmitter systems implicated in schizophrenia (like the dopamine system), remains, however, unknown. Here, we review molecular and cellular components of the dopamine system associated with postnatal neurogenesis and plasticity, both in rodents and in primates, and discuss their possible implication in schizophrenia. We focus mainly on the islands of Calleja, complex aggregations of granule cells in the ventral striatum, generated early postnatally in the subventricular zone. In contrast to the involution of the primate olfactory bulb, the islands of Calleja attain their maximal development in humans, an evolution paralleled by a larger ventral subventricular zone and more connections with other structures, including temporal cortical areas. The islands of Calleja express high levels of neuronal nitric oxide (NO) synthase and D3 dopamine receptors and are densely interconnected by dopaminergic projections with the ventral tegmental area. D3 receptors modulate subventricular zone neurogenesis and dopamine release. Their genetic deletion induces striatal hyperdopaminergia. We review data indicating a high plasticity of postnatal islands of Calleja, potentially facilitating susceptibility to schizophrenia-related risk factors. In this context, we propose a new pathophysiological model, where altered neurogenesis of the islands of Calleja may contribute to dysfunction of the dopamine and NO systems and psychosis through convergence of genetic and environmental disease-associated factors.

Key words: subventricular zone/islands of Calleja/D3 dopamine receptors/clozapine

Introduction

Schizophrenia is a chronic, highly debilitating neuropsychiatric disorder with presumed neurodevelopmental background¹ and teenage/young adult onset of symptoms. Therefore, pathologic changes during postnatal/juvenile development may be critical in triggering the delayed manifestation of schizophrenia. Susceptibility genes for schizophrenia, like *neuregulin-1* and *Disrupted-in-Schizophrenia 1 (DISC1)*, control postnatal and adult neurogenesis in the subventricular zone and dentate gyrus.²⁻⁵ However, it remains unclear if their potent effect on neurogenesis induces neurotransmitter (eg, dopamine) dysregulations associated with schizophrenia. Moreover, schizophrenia is a complex disease with disturbances located mainly in frontal brain areas that are not classical sites of neurogenesis (the prefrontal cortex, striatum, and nucleus accumbens). Focusing exclusively on the olfactory bulb, with low translational significance for humans, or on the dentate gyrus with sparse dopaminergic innervation⁶ may be insufficient to understand schizophrenia-associated dopaminergic alterations.

Secondary Neurogenesis And Migration Patterns From The Subventricular Zone

The subventricular zone is the main site of neurogenesis in early postnatal and adult life.⁷ Initially, it was thought that neuroblasts from the early postnatal subventricular zone migrate exclusively along the rostral migratory stream to the olfactory bulb.^{8,9} However, recent fate-mapping studies identified additional migratory routes (figures 1A–C). Accordingly, neuroblasts also disperse extensively into subcortical regions, in the so-called ventral migratory mass, generating, eg, the granule cells of the islands of Calleja.¹⁰ In fact, neuroblasts from the early postnatal subventricular zone

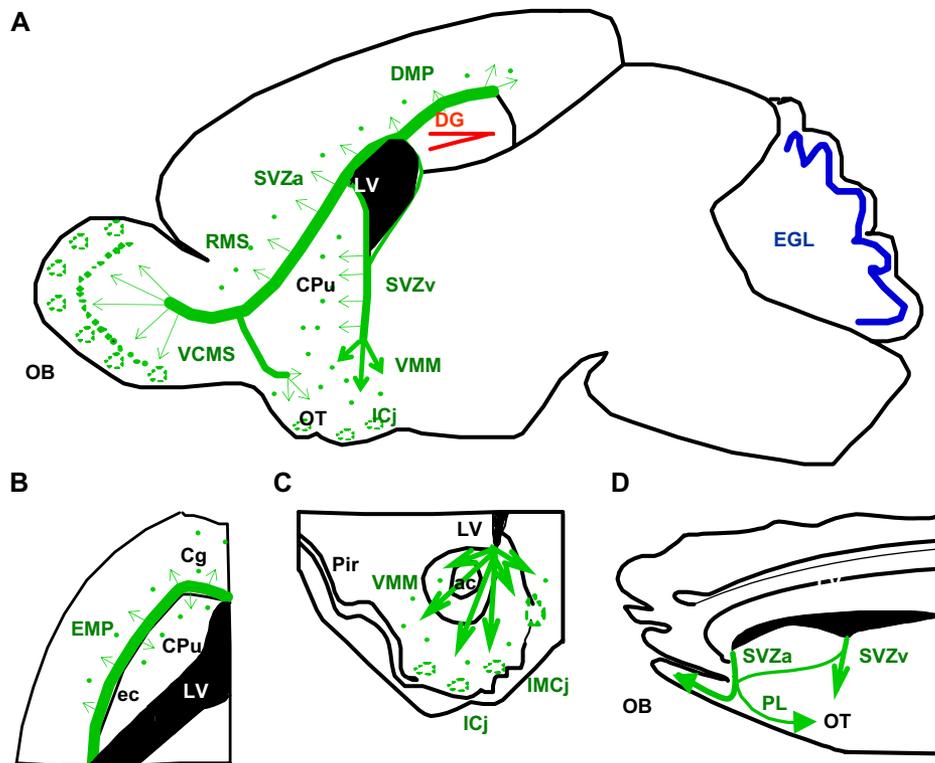


Fig. 1. Sites of Secondary Neurogenesis And Migration Pathways in The Postnatal And Adult Mammalian Brain. (A–C) Schematic representation of the pattern of secondary neurogenesis in the early postnatal rodent brain in sagittal (A), horizontal (B), and coronal sections (C). At early postnatal stages, migration of neuroblasts from the subventricular zone occurs not only to the olfactory bulb, in the rostral migratory stream, but also along the external capsule, forming the external migratory pathway, the alveus of the hippocampus, forming the dorsal migratory pathway, and dispersing into the striatum in the ventral migratory mass. The ventrocaudal migratory stream detaches from the rostral migratory stream caudally into the olfactory tubercle. (D) Migratory pathways of neuroblasts from the subventricular zone of adult squirrel monkeys represented in a sagittal section show, despite the involution of the olfactory bulb, striking similarities with the migratory pattern in the postnatal rodent brain. Neuroblasts and migratory streams originating in the subventricular zone are represented in green, neurogenesis in the dentate gyrus in red, and in the cerebellar external granular layer in blue (see references^{10–12}; see references in Supplementary Material.^{6,7} ac, anterior commissure; Cg, cingulate cortex; CPu, caudate-putamen; DMP, dorsal migratory pathway; DG, dentate gyrus; ec, external capsule; EGL, external granular layer; EMS, external migratory stream; ICj, islands of Calleja; IMCj, insula magna of Calleja; LV, lateral ventricle; Pir, piriform cortex; PL, posterior limb of the RMS; SVZa, anterior part of the subventricular zone; SVZv, ventral part of the subventricular zone; VCMS, ventrocaudal migratory stream.

migrate along all elongations of the callosal system into adjacent regions (the medial prefrontal cortex, striatum, and nucleus accumbens) and differentiate into specific GABAergic interneurons, similar to other granule cells.^{11,12}

This widespread early postnatal migratory pattern becomes restricted mainly to the rostral migratory stream in the adult.¹³ However, newborn neurons with similar morphology can be detected in the same limbic areas (including the islands of Calleja) in adult rats.^{14,15} Strikingly, in adult primates, neuronal migratory pathways from the subventricular zone, especially into subcortical areas, are similar to the migratory streams in young rodents, suggesting continuous neurogenesis in these areas (figure 1D; see Supplementary Material section).

An Example of Secondary Neurogenesis: The Islands of Calleja

The islands of Calleja represent accumulations of granule neurons in the ventral striatum, most likely GABAergic neurons, located at the pial border of the basal forebrain, with the major island at the medial border of the nucleus accumbens (figures 1A and 1C),^{16,17} representing in fact a single continuous complex structure¹⁸ of cells interconnected via gap junctions into a “functional syncytium.”¹⁹

The rodent islands of Calleja receive dense dopaminergic projections from the ventral tegmental area and the substantia nigra, topographically strictly separated in a medial vs a lateral division.²⁰ Their relation with mesencephalic dopaminergic neurons is bidirectional²⁰ (figure 2A). In primates, the input from the olfactory bulb to the islands of Calleja may be replaced by

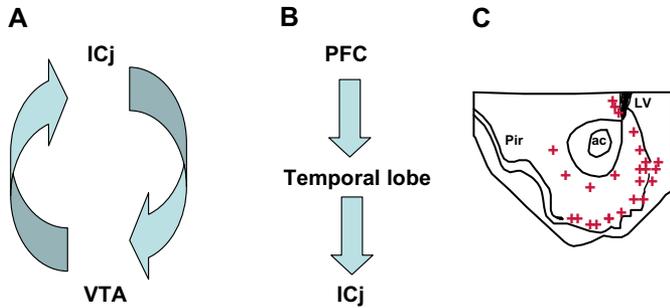


Fig. 2. Connections of the Islands of Calleja in Rodents (A) and Nonhuman Primates (B). Whereas the islands of Calleja (ICj) are connected in rodents bidirectionally with the ventral tegmental area (VTA) (A), the ICj in monkeys receive a direct projection from the temporal cortex, interconnected with other cortical areas such as the prefrontal cortex (PFC) (B). (C) Expression Pattern of D3 Receptors in The Frontal Brain. The highest expression occurs in the ICj and the subventricular zone, with a lower expression level in the shell of the nucleus accumbens. D3-expressing neurons are indicated by red crosses. ac, anterior commissure; LV, lateral ventricle; Pir, piriform cortex.

nonolfactory projections,²¹ with the rostral temporal lobe,²² allowing interconnections with the prefrontal cortex,²³ with potential relevance for schizophrenia (figure 2B).

The islands of Calleja express the highest level of dopamine D3 receptors, both in rodents²⁴ and in humans,²⁵ where it is found also in the ventral putamen, caudate, and globus pallidum.²⁶ D3 receptors show a specific expression pattern, mainly restricted to few limbic areas (figure 2C),²⁴ with abundant expression in the ventricular/subventricular zone (see Figure 3).²⁷ The system of reciprocal dopaminergic connections with the ventral tegmental area, with D3 receptors located postsynaptically and presynaptically (the latter with putative autoreceptor function),^{28,35} appears as a highly sensitive regulator of the extracellular dopamine level.

Besides the modulatory role on the dopamine system, other functions of the islands of Calleja are less understood. Similar to other granule cells, they contain also high levels of neuronal nitric oxide synthase (nNOS)^{36,37} and have been proposed to modulate the blood flow in the entire ventral striatum via NO production.³⁸ Moreover, they exhibit high levels of gonadotropic hormones and receptors and have been suggested as a regulatory system integrating reproductive behavior into cortical functions.³⁹

Implications for Schizophrenia

Gene-Environment Interactions With Possible Action on The Islands of Calleja

What could be the significance of an extended period of neurogenesis at postnatal and possibly adult stages for

Box 1. D3 dopamine receptors.

D3 receptors belong to the D2-like family of dopamine receptors, showing a specific high sensitivity to dopamine.²⁸ D3 receptors are the only dopamine receptors subtypes abundantly expressed in neuroepithelial cells during embryonic development.²⁷ They modulate also postnatal neurogenesis in the subventricular zone,²⁹ and their expression becomes restricted postnatally and in the adult to few brain areas in the ventral striatum (highest level in the islands of Calleja and the shell of the nucleus accumbens), cerebellum, and medial mammillary bodies.²⁷ BDNF and putative trophic factors released by ascending mesencephalic dopamine neurons modulate D3 receptor expression during development.³⁰ D3 receptor knockout mice show higher levels of striatal dopamine and increased locomotor activity.^{31,32,33,34}

Fig. 3. D3 Dopamine Receptors.

schizophrenia? Several environmental risk factors associated with schizophrenia act during early postnatal/juvenile life: perinatal hypoxia, cannabis consumption, and stress.⁴⁰ Even in the case of early embryonic triggers, structural changes affecting the dopamine system may occur during adolescence.⁴¹ A possible role of secondary neurogenesis in these changes has not been reported. Granule cells generated by secondary neurogenesis are particularly susceptible at postnatal/juvenile stages to noxious events affecting various steps of their development (proliferation, migration, differentiation, and integration into local circuits).^{42,43} The classic view of the “two-hit” hypothesis of schizophrenia⁴⁴ postulates that genetic factors determine early in embryonic development a “vulnerability” that remains silent until adulthood, when it becomes clinically manifest due to detrimental environmental factors (figure 4A). Susceptibility genes for schizophrenia, like *neuregulin-1* and *DISC1*, controlling postnatal/adult neurogenesis may exert their influence continuously during life (figure 4B). We hypothesize that, by acting on the islands of Calleja, genetic and environmental factors may contribute to dysregulations of the dopamine system, subsequent psychotic symptoms, and, over long-term periods, possible neurodegenerative changes via nNOS-mediated disturbances in local vasculature (figure 4C).

Potential Pathophysiological Mechanisms

According to our model, postnatal dysfunctional neurogenesis/dysgenesis of D3-expressing islands of Calleja may alter the system of reciprocal dopaminergic connections with the ventral tegmental area. A disturbance of D3 receptors may remove dopamine neurons from feedback control by dopamine, via postsynaptic and/or D3 receptors mesencephalic autoreceptors.^{35,45} Both pharmacological evidence⁴⁶ and analysis of D3 knockout mice^{31,32} support a role of D3 receptors in controlling dopamine release, showing elevated dopamine levels (twice

as high as in wild-type mice) in the nucleus accumbens and striatum of D3 knockout mice. The degree of hyperdopaminergia in D3 knockout mice may be even higher but is reduced by neuroadaptive mechanisms in these mice.⁴⁵ Interestingly, hyperdopaminergia in D3 knockout mice occurs also in the dorsal striatum, a region devoid of D3 receptors.³²

The hyperdopaminergia in D3 knockout mice, although less accentuated than in mice lacking the dopamine transporter (5-fold increase compared with wild-type mice),⁴⁷ supports a significant modulator role of D3 on dopamine release. Correspondingly, behavioral changes related to striatal hyperdopaminergia, like hyperlocomotion³³ and increased locomotor response to amphetamines,³⁴ are less evident (in some studies even absent^{48,49}) in D3 receptor knockout mice, compared with the extreme hyperactivity of dopamine transporter knockout mice.⁴⁷ Even if alterations of a D3 receptor deletion are not very accentuated, they may provide a “baseline” subclinical pathology, which may become clinically manifest in conjunction with additional triggers, like stress.

Interestingly, hyperdopaminergic tone in dopamine transporter knockout mice disturbs induction of prefrontal cortex long-term potentiation, possibly resulting in impaired executive functions.⁵⁰ Considering the low expression of dopamine transporter in the prefrontal cortex,⁵¹ the spill over of excessive striatal dopamine may cause these deficiencies seen in these mice.⁵⁰ It is unknown if similar alterations are caused by D3 receptor deficiency.

Not only dopaminergic pathways may be affected by postnatal/juvenile triggers. Considering the high expression of nNOS by the islands of Calleja and their proposed modulator role on blood flow in the ventral striatum,³⁸ disorders of their neurogenesis may induce local hypoperfusion. Such a scenario opens the possibility that postnatal alterations of a plastic structure induce long-term deficiencies in the ventral striatum, contributing to chronic symptoms of schizophrenia. Of note, early postnatal pharmacological inhibition of nNOS induces long-term social deficits, reversed by clozapine.⁵² Results in mice lacking nNOS are contradictory, reporting either decreased⁵³ or increased social interaction.⁵⁴

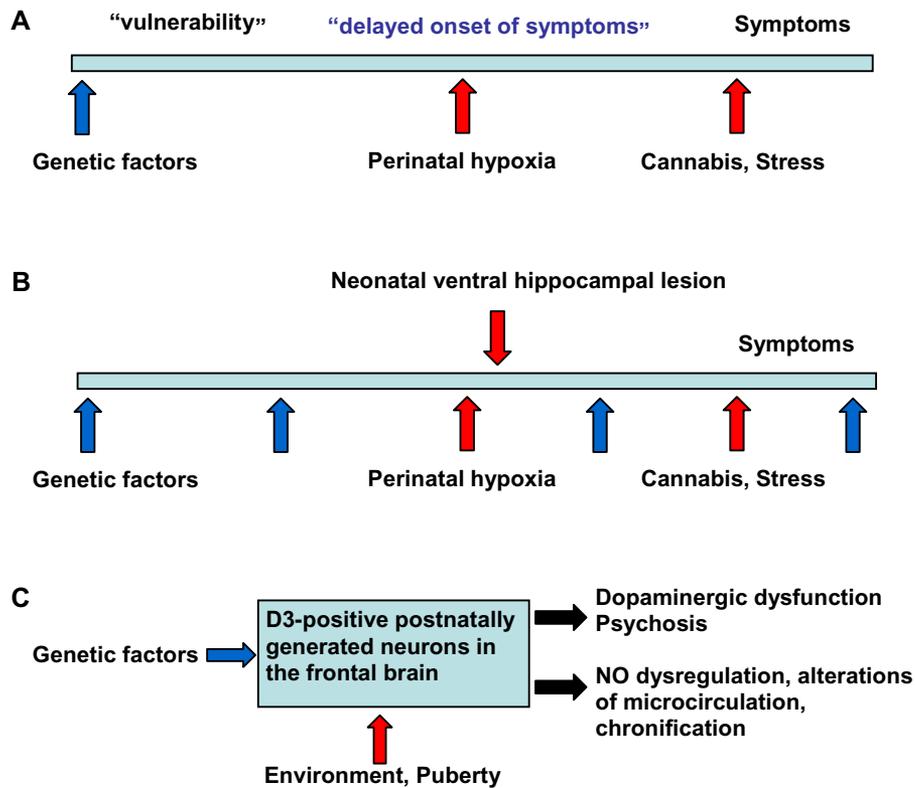


Fig. 4. Proposed Model for The Gene-Environment Interaction in Schizophrenia. (A, B) Schematic representation of the interaction between genetic factors (blue arrows) and environmental risk factors (red arrows) in schizophrenia. (A) The classic “two-hit” hypothesis postulates that gene defects act in early embryonic development, inducing a “vulnerability” that turns into psychosis in the adult due to environmental triggers. (B) Susceptibility genes for schizophrenia exert their influence also after birth, by regulating postnatal and adult neurogenesis, together with environmental factors. (C) Postnatally generated neurons in the frontal brain, dispersed or grouped in structures like the islands of Calleja, may represent the link between genetic and environmental factors and postnatal neurogenesis, triggering both acute psychotic and chronic neurodegenerative manifestations of the disease.

Perinatal Hypoxia And Alterations in Subventricular Zone Neurogenesis

Schizophrenia-associated environmental risk factors, acting on subventricular zone neurogenesis, may accentuate preexisting genetically induced dopaminergic dysregulations (figure 4C). Perinatal ischemia, eg, strongly affects subventricular zone neurogenesis, resulting in increased reactive cell proliferation and ectopic intrastriatal migration.²¹ Even prolonged periods of early postnatal hypoxia, causing extensive neuronal damage, are followed by a robust increase in subventricular zone cell proliferation.⁵⁵ However, this regeneration is dependent on factors sustaining neurogenesis (like specific growth factors) and is severely disrupted in their absence.⁵⁶ Possible consequences of this regeneration for structures formed at those stages, like the islands of Calleja, and consequently for the dopamine system have not been investigated. Importantly, in humans, decreased brain-derived neurotrophic factor (BDNF) levels at birth correlate with the risk of developing schizophrenia later.⁵⁷ This result appears important for the model presented here because BDNF modulates both neurogenesis and expression of D3 receptors.³⁰ Therefore, low levels of BDNF may impair regenerative posthypoxic neurogenesis and accentuate its effect, toward reaching the level of manifest symptoms. The role of other risk factors (stress, cannabis consume, gonadotropic hormones at puberty) in our model needs still to be determined.

Dopamine Dysregulation in The Neonatal Ventral Hippocampal Lesion Model

The pathways described here may correlate also with changes seen in the neonatal ventral hippocampal lesion model.⁵⁸ In this model, a lesion in the ventral hippocampus at postnatal day 7 (P7) induces hyperdopaminergic behavior, starting at P35 and being evident at P56.⁵⁹ Interestingly, among dopamine receptors, only the D3 subtype shows a strong progressive downregulation of expression in this model, starting at P41.⁶⁰ These results appear relevant for our model, considering the late neurogenesis/maturation and plasticity of D3-positive neurons. The mechanisms underlying these changes in this model are unknown. One possibility is that deafferentiation from the ventral hippocampus to the ventral striatum may disturb the integration and functionality of these late-generated neurons. Future studies need to determine the mechanisms underlying this selective effect on D3-expressing neurons.

The Islands of Calleja as Site of Antipsychotic Action

Our hypothesis may have implications not only regarding the pathogenesis but also the treatment of schizophrenia. While D3 receptors may have a role in plasticity in the nervous system, they are not considered to be a major

or common target of antipsychotic action. For example, D3 receptors are not generally occupied by all antipsychotics, eg, haloperidol and remoxipride have very low affinities for D3, unlike D2 receptors, which are consistently occupied by 50–80% at clinical doses.⁶¹ Interestingly, however, clozapine, unlike other antipsychotics, activates directly the islands of Calleja at high doses, as revealed by brain mapping using the immediate early gene *c-fos* in rodents⁶² and primates.⁶³ The involvement of D3 receptors or other receptors in mediating this effect is unclear.^{64–67} This specific effect raises the possibility that the unique role of clozapine in the therapy of negative and cognitive symptoms may occur by reversing defects in neurogenesis/plasticity in these structures.

Conclusions and Perspectives

Our model offers a dynamic view of pathogenic events in schizophrenia, opening the possibility for early therapeutic interventions. We wish to underline that our model may not be the only one contributing to dopamine dysregulation, being complementary to other mechanisms inducing dopamine alterations in the striatum of DISC1-mutant mice,⁶⁸ in frontal cortex neurons after pre/perinatal knockdown of DISC1⁶⁹ or after transient neonatal exposure to neuregulin-1.⁷⁰ We also acknowledge that several other neurodevelopmental mechanisms, eg, impacting on long- and short-range connectivity may be simultaneously active consequent to genetic risk for schizophrenia. Future studies should test both in animal models and in patients the molecular and cellular alterations proposed here. Regarding mechanisms relevant to schizophrenia, experiments in rodents may include analysis of the alterations at cellular level and of the systems presented here (dopamine, NO) in genetic models or in spatially restricted (eg, subventricular zone) ablations of susceptibility genes in interaction with environmental factors (like perinatal hypoxia). In patients, future experiments may include postmortem analysis of this structure and of relevant molecules (like D3 receptors and nNOS). All these investigations may contribute to a better understanding of the specific structures and molecular pathways implicated in schizophrenia.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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