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Review

Neuronal and brain morphological changes in animal models of schizophrenia

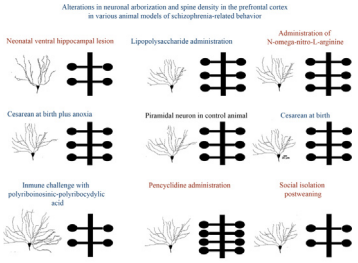
Gonzalo Flores [a,*], Julio César Morales-Medina [b], Alfonso Diaz [c]

[a] Laboratorio de Neuropsiquiatría, Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla. 14 Sur 6301, Puebla, 72570, Mexico
[b] Centro de Investigación en Reproducción Animal, CINVESTAV-IPN,—Universidad Autónoma de Tlaxcala, AP 62, 90000, Mexico
[c] Departamento de Farmacia, Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla. Puebla, 72570, Mexico

HIGHLIGHTS

- Schizophrenia produces neural remodeling in the prefrontal cortex in humans.
- Changes in the shape of dendritic arbor result of either gain or loss of connectivity.
- Animal models are useful tools to understand schizophrenia.
- Schizophrenia animal models present dendritic and spine density alterations.

GRAPHICAL ABSTRACT



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ABSTRACT

Schizophrenia, a severe and debilitating disorder with a high social burden, affects 1% of the adult world population. Available therapies are unable to treat all the symptoms, and result in strong side effects. For this reason, numerous animal models have been generated to elucidate the pathophysiology of this disorder. All these models present neuronal remodeling and abnormalities in spine stability. It is well known that the complexity in dendritic arborization determines the number of receptive synaptic contacts. Also the loss of dendritic spines and arbor stability are strongly associated with schizophrenia. This review evaluates changes in spine density and dendritic arborization in animal models of schizophrenia. By understanding these changes, pharmacological treatments can be designed to target specific neural systems to attenuate neuronal remodeling and associated behavioral deficits.

Abreviations: Ace, centromedial amygdala; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; CNS, central nervous system; DA, dopamine; DAD2R, DA D2 receptor; DAT, dopamine transporter; DG, dentate gyrus; DH, dorsal hippocampus; GD, gestational day;; HPA, hypothalamic–pituitary–adrenal axis; IH, intermediate hippocampus; IL-1 β, interleukin 1β; KO, knock-out; LPS, lipopolysaccharide; mPFC, medial PFC; N-LNNA, *N*-omega-nitro-L-arginine; NAcc, nucleus accumbens; NO, nitric oxide; nPFCL, neonatal prefrontal cortex lesion; PCP, phencyclidine; PD7, postnatal day 7; PFC, prefrontal cortex; poly I:C, polyriboinosinic-polyribocydylic acid; PTSD, posttraumatic stress disorder; PWSI, post weaning social isolation; SNc, substantia nigra pars compacta; TDL, total dendritic length; TNF-α, tumor necrosis factor alpha; VH, ventral hippocampus; VTA, ventral tegmental area.

* Corresponding author. Fax: +52 222 2295500, ext. 7301.
E-mail addresses: gonzalo.flores@correo.buap.mx, gonzaloflores56@gmail.com (G. Flores).

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Contents

1. Schizophrenia

Schizophrenia is a devastating disorder not only for the patient but also for the family. Indeed, this disorder alters the relation between the patient and the family and could induce a family breakdown modifying the prognostic of the schizophrenic patient. This complex disorder affects 1% of the world's population. Interestingly, this mental disorder starts in early adulthood during the time when synapses are pruned [1,2] with a particular combination of positive, negative, affective symptoms as well as cognitive deficits. The severity of these symptoms can change over time depending on the disease stage [1,2]. Positive symptoms include hallucinations, delusions and thought disorders; negative symptoms comprise flat emotional expression, poor quality of speech, inability to derive pleasure from activities previously enjoyable and inability to initiate and persist in goal-directed activities. Finally, cognitive symptoms include deficits in executive functioning, attention and working memory.

The neural mechanisms of schizophrenia are not yet fully known, and available pharmacological treatments are often ineffective to bring back the schizophrenic patient to normal functionality. In recent years, dendritic morphological studies using the Golgi and Golgi-Cox procedures (Fig. 1) have demonstrated changes in arborization and dendritic spine density in limbic regions such as prefrontal cortex (PFC), hippocampus and amygdala in postmortem tissue from schizophrenic patients and in animal models of schizophrenia [1,3,4]. These studies suggest that schizophrenia may involve dendritic spine abnormalities. In addition, recently a structural and biochemical study reported synaptic pathology in postmortem PFC tissue of schizophrenic patients using multiple label fluorescence confocal microscopy [5].

2. Neuronal staining as a tool to evaluate neuronal morphology

The so-called Golgi–Cox method is a histological technique widely used as a tool to study neurons in the central nervous system (CNS). This staining procedure together with the Sholl analysis for light microscopy provides information about morphology, distribution, location, and intrinsic connections of neurons. Although this method does not reveal details of the internal structure of nerve cells, it does provide a unique view of the entire neurons and the relation of dendrites and axons to the neuron body, associated with their functional role in the normal CNS, for full details see the following book chapter [6].

The chromate precipitate staining was discovered by Camilo Golgi, when he observed that the whole neuron looked black and entitled this procedure as "black reaction". There are two major groups of techniques using chromate precipitations known respectively as the Golgi (silver chromate) and Golgi-Cox (mercury chromate). Strangely, the Golgi-Cox staining is a better method than the Golgi procedure, especially to demonstrate the dendritic architecture of neurons in the mammalian brain [7].

3. Relevance of neuronal morphology in schizophrenia

Neuronal rearrangement and alterations in dendritic spines are observed in postmortem brains of patients with schizophrenia and numerous animal models of schizophrenia-like behavior [4] however, their causes have yet to be established [6–8]. For example, a reduced dendritic spine number has been reported in the layer 3 of the PFC in schizophrenia [9–12] and this region is a major site for cortico-cortico and thalamo-cortico integration [4].

The shape of dendritic arbor of a neuron determines the number and distribution of receptive synaptic contacts [13]. Moreover, dendritic arbors are dynamic during development, extend and retract