Nitric oxide (NO) is an inter- and intra-cellular messenger[25] involved in physiological processes including synaptic and neuronal plasticity[26]. Moreover, schizophrenic subjects present increased level of plasma NO[27]. The nVHL rat also presents increased levels of NO[28] as well as increased nitric oxide synthase (NOS) immunostaining in the PFC[29]. In fact, NO has emerged as a key player to understand the neurochemical abnormalities observed in the nVHL rat. It has been established that NO interacts with DA and glutamate neurotransmitters[30].

Animals that underwent the nVHL also present dysregulated proteins such as clathrin light chain B, a protein important for the expression of synaptophysin after puberty[31]; low level of nerve growth factor inducible-B mRNA[32] and reduced expression of brain-derived neurotrophic factor (BDNF) mRNA[33]. In apparent agreement, patients with schizophrenia also exhibit these neurochemical alterations in the PFC including low expression of synaptophysin[34] and decreased immunoreactivity to BDNF[35,36]. Consequently, all these neurotransmitters, growth factors and proteins have an impact on the synaptic connections that ultimately reshape neurons in the PFC.

Neuromorphological alterations

In postmortem brains of patients with schizophrenia, Garey et al.[37] observed reduced spine number in PFC layer III pyramidal neurons. While Koleske[38] indicated that the shape of dendritic arbor determines the number and distribution of receptive synaptic contacts; Fiala et al.,[39] suggested that the dendritic spines are the main sites of excitatory input. Therefore alterations in spine density or dendritic arbor are associated with gain or loss of connectivity. Our group has shown a decrease in dendritic length and dendritic spines not only in the PFC layer V but also layer III in the nVHL rat[28,40,41]. The neuronal hypotrophy observed in PFC neurons has been associated with lack of input from the ventral hippocampus at a critical stage of development[1].

Earlier disconnection (PD7 – PD9) of the ventral hippocampus and PFC pathway causes behavioral, neurochemical and neuromorphological changes after puberty or in early adulthood, which does not manifest itself if the damage had occurred before PD14[42]. All this implies that there is a window of time in which the injury of this pathway may cause permanent damage. Moreover, the neonatal lesion of PFC, also causes changes in behavior, neurochemistry and morphology[40,43-45], however these changes are not as copious as in the case of nVHL animals. Interestingly, at adult age, lesion of the PFC in nVHL animals, ameliorate behavioral changes[46]. Moreover, earlier lesion of VH altered the physiological response of PFC pyramidal neurons after puberty, which exhibited excessive firing in response to mesocortical stimulation[13]. Therefore, earlier disruption of the VH and PFC pathway affected the function of PFC after puberty, such as reduced levels of the BDNF in the PFC of the nVHL rats[47].

Conclusions

The nVHL rat presents neurochemical and neuroanatomical alterations in the PFC similar to those observed in schizophrenic patients. Early on, O'Donnell[48] stated that "disinhibited PFC could be responsible for cognitive deficits observed in schizophrenia". Moreover, PFC refinement occurs during late adolescence[49] and the behavioral deficits in this animal model are also observed only after this period. Further investigations in this animal model are required to understand the pathology of this devastating disorder as well as to test potential novel drugs for the treatment of different deficits observed in schizophrenia.

Acknowledgements

GF and JCMM acknowledge the membership of National Research System of Mexico. JCMM is a recipient of International Brain Research Organization Return Home fellowship. We thank Mira Thakur for proofreading the manuscript.

References

1. Flores G, Morales-Medina JC, Diaz A. Neuronal and brain morphological changes in animal models of schizophrenia. Behavioural Brain Res. 2016; 301:190-203
2. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry. 2000; 57:65-73.
3. Tseng KY, Chambers RA, Lipska BK. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. Behavioural Brain Res. 2009; 204:295-305.
4. Weinberger DR, Aloia MS, Goldberg TE, Berman KF. The frontal lobes and schizophrenia. J Neuropsychiatry & Clinical Neurosci. 1994; 6:419-427.
5. Alvarez-Bolado G, Celio MR. The ventrolateral hypothalamic area and the parvafox nucleus: Role in the expression of (positive) emotions? J Comp Neurol. 2016; 524:1616-1623.
6. Mueser KT, Penn DL, Blanchard JJ, Bellack AS. Affect recognition in schizophrenia: a synthesis of findings across three studies. Psychiatry. 1997; 60:301-308.
7. Bortolon C, Capdevielle D, Raffard S. Face recognition in schizophrenia disorder: A comprehensive review of behavioral, neuroimaging and neurophysiological studies. Neurosci Biobehav Rev. 2015; 53:79-107
8. Tseng KY, Lewis BL, Lipska BK, O'Donnell P. Post-pubertal disruption of medial prefrontal cortical dopamine-glutamate interactions in a developmental animal model of schizophrenia. Biol Psychiatry. 2007; 62:730-738.
9. Belujon P, Patton MH, Grace AA. Role of the prefrontal cortex in altered hippocampal-accumbens synaptic plasticity in a developmental animal model of schizophrenia. Cereb Cortex. 2014; 24:968-977
10. Banks PJ, Burroughs AC, Barker GR, Brown JT, Warburton EC, Bashir ZI. Disruption of hippocampal-prefrontal cortex activity by dopamine D2R-dependent LTD of NMDAR transmission. Proc Natl Acad Sci U S A. 2015; 112:11096-11101

11. Flores G, Atzori M. The Potential of Cerebrolysin in the Treatment of Schizophrenia. Pharmacol. Pharm. 2014; 5, 691–704.

12. Lipska BK, Weinberger DR. To model a psychiatric disorder in animals: schizophrenia as a reality test. Neuropsychopharmacology. 2000; 23:223-239.

13. O'Donnell P, Lewis BL, Weinberger DR, Lipska BK. Neonatal hippocampal damage alters electrophysiological properties of prefrontal cortical neurons in adult rats. Cereb Cortex. 2002; 12:975-982.

14. Manitt C, Mimee A, Eng C, et al. The netrin receptor DCC is required in the pubertal organization of mesocortical dopamine circuitry. J Neurosci. 2011; 31:8381-8394.

15. Al-Amin HA, Shannon Weickert C, Weinberger DR, Lipska BK. Delayed onset of enhanced MK-801-induced motor hyperactivity after neonatal lesions of the rat ventral hippocampus. Biological Psychiatry. 2001; 49:528-539.

16. Howes O, McCutcheon R, Stone J. Glutamate and dopamine in schizophrenia: an update for the 21st century. J Psychopharmacol. 2015; 29:97-115.

17. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nat Rev Neurosci. 2016; In press

18. Alquicer G, Silva-Gomez AB, Peralta F, Flores G. Neonatal ventral hippocampus lesion alters the dopamine content in the limbic regions in postpubertal rats. Int J Dev Neurosci. 2004; 22:103-111.

19. Tseng KY, O'Donnell P. Dopamine-glutamate interactions controlling prefrontal cortical pyramidal cell excitability involve multiple signaling mechanisms. J Neurosci. 2004; 24:5131-5139.

20. Laplante F, Srivastava LK, Quirion R. Alterations in dopaminergic modulation of prefrontal cortical acetylcholine release in post-pubertal rats with neonatal ventral hippocampal lesions. J Neurochem. 2004; 89:314-323

21. Macedo CE, Angst MJ, Gobaille S, Schleef C, Guignard B, Guiberteau T, Louilot A, Sandner G. Prefrontal dopamine release and sensory-specific satiety altered in rats with neonatal ventral hippocampal lesions. Behav Brain Res. 2012; 231:97-104.

22. Taylor SF, Tso IF. GABA abnormalities in schizophrenia: a methodological review of in vivo studies. Schizophr Res. 2015; 167:84-90.

23. Chiapponi C, Piras F, Caltagirone C, Spalletta G. GABA System in Schizophrenia and Mood Disorders: A Mini Review on Third-Generation Imaging Studies. Frontiers Psychiatry. 2016; 7:61.

24. Ryan RT, Bhardwaj SK, Tse YC, Srivastava LK, Wong TP. Opposing alterations in excitation and inhibition of layer 5 medial prefrontal cortex pyramidal neurons following neonatal ventral hippocampal lesion. Cereb Cortex. 2013; 23:1198-1207

25. Garthwaite J, Charles SL, Chess-Williams R. Endothelium-derived relaxing factor release on activation of NMDA receptors suggests role as intercellular messenger in the brain. Nature. 1988; 336:385-388.

26. Prast H, Philippu A. Nitric oxide as modulator of neuronal function. Prog Neurobiol. 2001; 64:51-68.

27. Yanik M, Vural H, Kocyigit A, et al. Is the arginine-nitric oxide pathway involved in the pathogenesis of schizophrenia? Neuropsychobiology. 2003; 47:61-65.

28. Bringas ME, Morales-Medina JC, Flores-Vivaldo Y, et al. Clozapine administration reverses behavioral, neuronal, and nitric oxide disturbances in the neonatal ventral hippocampus rat. Neuropharmacology. 2012; 62:1848-1857.

29. Bernstein HG, Grecksch G, Becker A, Hollt V, Bogerts B. Cellular changes in rat brain areas associated with neonatal hippocampal damage. Neuroreport. 1999; 10:2307-2311.

30. Bernstein HG, Keilhoff G, Steiner J, Dobrowolny H, Bogerts B. Nitric oxide and schizophrenia: present knowledge and emerging concepts of therapy. CNS Neurol Disord Drug Targets. 2011; 10:792-807.

31. Vercauteren FG, Flores G, Ma W, et al. An organelle proteomic method to study neurotransmission-related proteins, applied to a neurodevelopmental model of schizophrenia. Proteomics. 2007; 7:3569-3579.

32. Bhardwaj SK, Beaudry G, Quirion R, Levesque D, Srivastava LK. Neonatal ventral hippocampus lesion leads to reductions in nerve growth factor inducible-B mRNA in the prefrontal cortex and increased amphetamine response in the nucleus accumbens and dorsal striatum. Neuroscience. 2003; 122:669-676.

33. Lipska BK, Khaing ZZ, Weickert CS, Weinberger DR. BDNF mRNA expression in rat hippocampus and prefrontal cortex: effects of neonatal ventral hippocampal damage and antipsychotic drugs. Eur J Neurosci. 2001; 14:135-144.

34. Glantz LA, Lewis DA. Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia. Regional and diagnostic specificity. Arch Gen Psychiatry. 1997; 54:660-669.

35. Ray MT, Shannon Weickert C, Webster MJ. Decreased BDNF and TrkB mRNA expression in multiple cortical areas of patients with schizophrenia and mood disorders. Transl Psychiatry. 2014; 4:e389.

36. Reinhart V, Bove SE, Volfson D, Lewis DA, Kleiman RJ, Lanz TA. Evaluation of TrkB and BDNF transcripts in prefrontal cortex, hippocampus, and striatum from subjects with schizophrenia, bipolar disorder, and major depressive disorder. Neurobiol Dis. 2015; 77:220-227.

37. Garey LJ, Ong WY, Patel TS, et al. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J Neurol Neurosurg Psychiatry. 1998; 65:446-453.

38. Koleske AJ. Molecular mechanisms of dendrite stability. Nat Rev Neurosci. 2013; 14:536-550.

39. Fiala JC, Spacek J, Harris KM. Dendritic spine pathology: cause or consequence of neurological disorders? Brain research Brain Res Rev. 2002; 39:29-54.

40. Flores G, Alquicer G, Silva-Gómez AB, et al. Alterations in dendritic morphology of prefrontal cortical and nucleus accumbens neurons in post-pubertal rats after neonatal excitotoxic lesions of the ventral hippocampus. Neuroscience. 2005; 133:463-470.

41. Vazquez-Roque RA, Ramos B, Tecuatl C, et al. Chronic administration of the neurotrophic agent cerebrolysin ameliorates the behavioral and morphological changes induced by neonatal ventral hippocampus lesion in a rat model of schizophrenia. Journal of Neuroscience Res. 2012; 90:288-306.

42. Wood GK, Liang JJ, Flores G, Ahmad S, Quirion R, Srivastava LK. Cloning and in situ hybridization analysis of the expression of polysialyltransferase mRNA in the developing and adult rat brain. Brain Res Mol Brain Res. 1997; 51:69-81.

43. Flores G, Barbeau D, Quirion R, Srivastava LK. Decreased binding of dopamine D3 receptors in limbic subregions after neonatal bilateral lesion of rat hippocampus. J Neurosci. 1996; 16:2020-2026.

44. Brake WG, Flores G, Francis D, Meaney MJ, Srivastava LK, Gratton A. Enhanced nucleus accumbens dopamine and plasma corticosterone stress responses in adult rats with neonatal excitotoxic lesions to the medial prefrontal cortex. Neuroscience. 2000; 96:687-95.

45. Lazcano Z, Solis O, Díaz A, Brambila E, Aguilar-Alonso P, Guevara J, et al. Dendritic morphology changes in neurons from the ventral hippocampus, amygdala and nucleus accumbens in rats with neonatal lesions into the prefrontal cortex. Synapse. 2015; 69:314-25

46. Goto Y, O'Donnell P. Prefrontal lesion reverses abnormal mesoaccumbens response in an animal model of schizophrenia. Biol Psychiatry. 2004; 55:172-6.

47. Molteni R, Lipska BK, Weinberger DR, Racagni G, Riva MA. Developmental and stress-related changes of neurotrophic factor gene expression in an animal model of schizophrenia. Mol Psychiatry. 2001; 6:285–292.

48. O'Donnell P. Cortical disinhibition in the neonatal ventral hippocampal lesion model of schizophrenia: new vistas on possible therapeutic approaches. Pharmacol Ther. 2012; 133:19-25.

49. Manitt C, Eng C, Pokinko M, Ryan RT, Torres-Berrio A, Lopez JP, et al. dcc orchestrates the development of the prefrontal cortex during adolescence and is altered in psychiatric patients. Transl Psychiatry. 2013; 3:e338.