



Département de psychiatrie
Centre de neurosciences psychiatriques
Site de Cery
CH-1008 Prilly - Lausanne

Centre de Neurosciences Psychiatriques

CNP SEMINAR

ANNOUNCEMENT

Friday, June 10, 2011, 11:00

“Fast-Spiking Pathways to Schizophrenia”

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The fast-spiking parvalbumin-positive (PV+) neuronal system is directly involved in the generation of gamma oscillatory activity in brain, and is essential for shaping neuronal circuits during postnatal brain development. Discrete functional disruptions in this GABAergic system will alter the excitatory/inhibitory balance in brain, and this alteration may be at the origins of the cognitive deficiencies observed in schizophrenia. Indeed, evidence derived from schizophrenia postmortem brain tissue and rodent models support the hypothesis of a specific dysfunction of PV+ neurons in the etiology of the disease. However, when these deficiencies occur and whether they are cause or consequence of the disease is still unknown.

Our work has shown that repetitive exposure of rodents to ketamine, an NMDA receptor antagonist, leads to reversible neurochemical and behavioral changes in adult rodents that resemble those found in schizophrenia patients. Ketamine increases brain levels of IL-6 and activates the superoxide-producing enzyme NADPH oxidase (Nox2). This, in turn, produces a lasting redox imbalance in brain that leads to a reversible loss of the GABAergic phenotype of PV+ neurons and to decreased inhibitory activity in prefrontal of adult rodents.

When activation of the IL-6/Nox2 pathway occurs during the perinatal period it leads to a permanent loss of PV expression in PV+ neurons, and to a decreased response of the interneurons to excitatory transmission. At the systems level, it leads to pronounced alterations in auditory evoked related potentials. This alteration resemble what is observed in schizophrenia patients, and suggest that activation of the IL-6/Nox2 pathway during early life may alter the normal development of PV+ neurons leading to schizophrenia symptoms in late adolescence and early adulthood.

Recent publications

1. *Ketamine-induced loss of phenotype of fast-spiking interneurons is mediated by NADPH-oxidase.* Behrens MM, Ali SS, Dao DN, Lucero J, Shekhtman G, Quick KL, Dugan LL. *Science*. 2007 Dec 7;318(5856):1645-7.
2. *Interleukin-6 mediates the increase in NADPH-oxidase in the ketamine model of schizophrenia.* Behrens MM, Ali SS, Dugan LL. *J Neurosci*. 2008 Dec 17;28(51):13957-66.
3. *Behavioral and neurochemical consequences of cortical oxidative stress on parvalbumin-interneuron maturation in rodent models of schizophrenia.* Powell SB, Sejnowski TJ, Behrens MM. *Neuropharmacology*. 2011 Feb 17. [Epub ahead of print]