

Neurobiology of severe mental disorders: from cell to bedside

25th International Symposium of the Centre de recherche en sciences neurologiques, Université de Montréal

Pierre-Paul Rompré, PhD; Emmanuel Stip, MD; Louis-Éric Trudeau, PhD

Rompré, Stip — Department of Psychiatry, Université de Montréal, and Centre de Recherche Fernand Seguin, l'Hôpital Louis-H. Lafontaine, Montréal; Stip, Trudeau — Department of Pharmacology, Université de Montréal, Montréal, Que.

This and the next issue of the *Journal of Psychiatry and Neuroscience* include review articles written by leading scientists who participated in an international symposium entitled "Neurobiology of severe mental disorders: from cell to bedside" that was held in Montréal on May 4-5, 2003. Six of the review articles focus on the neurobiology of major depression, and 3 focus on the neurobiology of schizophrenia (see www.crsn.umontreal.ca/XXVs/program.html for further details about the symposium).

Selective serotonin (5-HT) reuptake inhibitors (SSRIs) are the current treatments of choice for major depression. Their mechanisms of action have until recently guided most of the research aimed at understanding the neurobiologic bases of this disorder. Electrophysiologic and neurochemical experiments performed mainly on rodents revealed that these compounds act presynaptically and postsynaptically to alter in a time-dependent manner noradrenergic and/or serotonergic neurotransmission in limbic brain regions implicated in emotional responses. Celada et al¹ review these mechanisms and extend them to cortico-limbic circuitry that comprises feedback loops to brain-stem

serotonergic nuclei and is modulated by different subtypes of 5-HT receptors. They also describe mechanisms that contribute to increased clinical effectiveness and shortened onset of action of SSRIs.

Although the role of norepinephrine (NE) and 5-HT in the action of antidepressant drugs is well supported by empirical findings, other neurotransmitter systems also come into play. As clearly outlined by several participants at the symposium, major depression involves a very complex network of neuronal and nonneuronal elements that mediate the no-less-complex clinical phenotype. Blier et al² describe electrophysiologic and neurochemical studies (performed on normal and knock-out rodents) that show that a neurokinin, substance P, acts on NE neurons to modulate 5-HT neurotransmission. Despite the mixed findings of clinical trials with neurokinin antagonists, further research is warranted to provide a clear understanding of the modulation of limbic neurotransmission by substance P. This may lead to a new therapeutic strategy that potentiates the clinical effectiveness of SSRIs, or to the development of a new antidepressant treatment mostly devoid of deleterious side effects, or both.

Correspondence to: Dr. Louis-Éric Trudeau, Department of Pharmacology, Université de Montréal, CP 6128, Succursale Centre-ville, Montréal QC H3C 3J7; fax 514 343-2291; louis-eric.trudeau@umontreal.ca

Medical subject headings: antidepressive agents; depression; models, animal; schizophrenia; serotonin uptake inhibitors.

J Psychiatry Neurosci 2004;29(3):167-9.

Stress exerts a complex set of effects on the human organism and particularly on the central nervous system. Although it can be beneficial in some cases, it is thought to be an important factor in precipitating depression in vulnerable individuals. One of the major physiologic phenomena associated with stress is activation of the hypothalamic–pituitary–adrenal (HPA) axis. The relevance of this system to affective disorders is reviewed by Barden,³ who describes a series of studies that take advantage of genetic methods to provide support for a role of corticotropin and glucocorticoids in the behavioural phenotype of depression and in the mechanisms of action of antidepressant drugs. His findings suggest that these drugs act on transcription mechanisms to restore brain controls of homeostatic functions of the HPA axis. In the same vein, Malberg⁴ describes the relevance of neurogenesis (neuron and glial cells) to depression and its link to the HPA axis response via glucocorticoids. She reviews basic and clinical data showing that cell atrophy in the hippocampus is correlated with depression, is initiated in animals by stressful conditions that lead to depression-like behavioural phenotypes and is reversed by pharmacologic and non-pharmacologic antidepressant treatments. She reports that antidepressant treatments selectively induce neurogenesis and promote cell survival with a time course that approaches that of clinical responses. Together, these findings provide new important insights into the neurobiologic bases of the disorder and open new avenues for treatments that target not only primary symptoms but also the progression of the disorder.

Major depression is indeed an emotional disorder, but it is also a cognitive disorder. The basic cortical mechanisms described by Celada et al¹ are likely to account for the changes in cognitive functions initiated by SSRIs. Paus and Barrett⁵ review in more detail cognitive functions that are altered in depression and the cortical substrate(s) underlying, at least in part, some of these deficits. They provide a review of the application of a new, noninvasive treatment for depression, namely, repetitive transcranial magnetic stimulation, that may constitute a relevant alternative treatment to electroconvulsive therapy for a subpopulation of patients. This approach also has the potential to provide new insights into the functional neuroanatomy and neurochemistry (when combined with positron emission tomography) of cognitive deficits in depression.

The genetic basis of depression still remains unclear, but the recent characterization of the human genome

provides new hope. As clearly argued by Lesch,⁶ major depression, just like schizophrenia and other mental disorders (anxiety, neurodevelopmental disorders), results from a complex interaction of genotype, phenotype and the environment. Development of new research methods, such as microarrays and conditional knockout and knockin (overexpression) techniques, will shed light on these complex interactions. Studies in nonhuman primates provide empirical evidence in support of tight genetic–environment interactions in the development of abnormal behavioural responses and their neurobiologic bases.

Although hotly investigated for more than 50 years, the neurobiologic basis of schizophrenia remains in large part a mystery. Because of the discovery that antipsychotic drugs act as dopamine receptor antagonists, the bulk of research efforts has focused on identifying the genetic, cellular and morphological basis of disruptions of the central dopamine system in schizophrenia. Although the dopamine system is certainly implicated in the symptoms of schizophrenia, new research efforts in the last decade have identified alternative and complementary suspects including the neurotransmitter glutamate and its receptors. A special section of the Montréal symposium addressed such new research directions by asking the following question: Should we not look “beyond monoamines”? This is a recurring theme in the 3 review articles that deal with schizophrenia. In their review of the pathophysiology of schizophrenia, Perlman et al⁷ note that new insights into our understanding of the perturbations of prefrontal cortex glutamate neurons and related subcortical structures in schizophrenia are likely to come from postmortem investigations that combine anatomical and molecular approaches with a genetic approach based on the identification of a number of candidate schizophrenia susceptibility genes.

As in most areas of medicine, progress in improving treatments or in identifying new therapeutic approaches is greatly facilitated by the development of animal models. Because schizophrenia is largely a disease of cognition, developing a suitable animal model has long been and still is a major hurdle for modern research. In her review of the use of animal models to test the neurodevelopmental hypothesis of schizophrenia, Lipska⁸ describes recent progress in this direction. In particular, she proposes a model that goes “beyond monoamines” in that it does not implicate a direct manipulation of the dopamine system. Rather, transient

interruption of neural activity in the hippocampus of neonatal rodents is shown to produce a delayed perturbation of cortical glutamatergic neurons and indirectly of subcortical circuits. It is proposed that these features partly mimic the progression of schizophrenia symptoms. The model is inclusive and, interestingly, not limited to hypothesizing a primary deficit within the mesocorticolimbic dopamine system. Finally, an interesting new twist on the possible roles of dopamine and glutamate in the pathophysiology of schizophrenia is highlighted by Trudeau,⁹ who summarizes mounting evidence from animal research that shows that dopamine-containing neurons in the brain most likely have the capacity to use glutamate as a co-transmitter. Together with similar findings suggesting co-release of glutamate with serotonin, the possible involvement of changes in the neurotransmitter phenotype of monoamine neurons in conditions such as schizophrenia and depression appears to be a promising new direction for future research.

Together, the studies described in these review articles provide clear evidence that research is progressing at a fast rate. Hopefully, new findings generated in the next decade will provide a solid footing for the development of new treatment strategies that will be effective in a larger proportion of patients and possibly take us beyond symptom management.

We would like to dedicate this special issue to the memory of our colleague Dr. Tomás A. Reader, who participated in the initial organization of this symposium but left us in May 2002, a year before it took place. Tomás was a professor of physiology at the Université de Montréal. He made significant contributions to the field of neuropsychopharmacology and, particularly, to our understanding of the mechanisms of action of psychotropic medications. He was also an active member of the Canadian College of Neuropsychopharmacology.

Acknowledgements: This symposium was organized thanks to the financial support of the following companies: Wyeth, Janssen-Ortho, Pfizer, Bristol-Myers Squibb Canada, AstraZeneca, Servier Canada, as well as the Ministères des Finances et du Développement économique et régional et de la Recherche du Québec and the Canadian Institutes of Health Research.

Competing interests: None declared for Drs. Rompré and Trudeau. Dr. Stip is on the advisory boards of Pfizer, Eli Lilly, AstraZeneca and Janssen and has received research funding from Novartis and AstraZeneca, speaker fees from Pfizer, Eli Lilly and AstraZeneca and travel assistance from Pfizer, Eli Lilly, AstraZeneca, Janssen and Novartis.

References

1. Celada P, Puig MV, Amargós-Bosch M, Adell A, Artigas F. The therapeutic role of 5-HT_{1A} and 5-HT_{2A} receptors in depression. *J Psychiatry Neurosci*. In press.
2. Blier P, Gobbi G, Haddjeri N, Santarelli L, Mathew G, Hen R. Impact of substance P receptor antagonism on the serotonin and norepinephrine systems: relevance to the antidepressant/anxiolytic response. *J Psychiatry Neurosci* 2004;29(3):208-18.
3. Barden N. Implication of the hypothalamic-pituitary-adrenal axis in the pathophysiology of depression. *J Psychiatry Neurosci* 2004;29(3):185-93.
4. Malberg J. Implications of adult hippocampal neurogenesis in antidepressant action. *J Psychiatry Neurosci* 2004;29(3):196-205.
5. Paus T, Barrett J. Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. *J Psychiatry Neurosci*. In press.
6. Lesch KP. Gene-environment interaction and the genetics of depression. *J Psychiatry Neurosci* 2004;29(3):174-84.
7. Perlman WR, Weickert CS, Akil M, Kleinman JE. Postmortem investigations of the pathophysiology of schizophrenia: the role of susceptibility genes. *J Psychiatry Neurosci*. In press.
8. Lipska BK. Using animal models to test a neurodevelopmental hypothesis of schizophrenia. *J Psychiatry Neurosci*. In press.
9. Trudeau LE. Glutamate co-transmission as an emerging concept in monoamine neuron function. *J Psychiatry Neurosci*. In press.