Moving past the "neuroncentric" perspective: a role for glia in neuropsychiatric disorders

Aaron Y. Lai, BSc; Kamaldeep S. Dhami, BSc; Kathryn G. Todd, PhD

Lai, Dhami, Todd — Neurochemical Research Unit, Department of Psychiatry and Centre for Neuroscience, University of Alberta, Edmonton, Alta.

The development of neuropsychiatric disorders involves an array of different underlying mechanisms, many of which remain at the level of hypotheses and thus the centre of much debate. These mechanisms range from subtle changes in neurochemistry (e.g., the monoamine hypothesis of depression) to cell death (e.g., the death of cholinergic neurons in Alzheimer disease). More often than not, a single disorder requires several hypotheses to explain satisfactorily the underlying etiological mechanisms. Even a decade ago, glial cells were seldom considered in the function of the normal or pathological brain. In the "neuroncentric" past of neuroscience, glial cells were often overlooked or relegated to an undefined supportive role, and, in the diseased state, glia were rarely viewed as culprits responsible for the development of the disease. We now know that glial cells are integral to the development of the central nervous system, that they are critical to normal brain function and that they play a key role in the pathogenesis of many brain disorders. Glial cells, especially microglia, are responsive by nature; they sense and react to signals from diseased neurons. Microglia, the resident immune cells of the brain, are a critical component of neuroinflammation, during which they sense central nervous system abnormalities and become activated. Activated microglia can change their morphology, increase their production of cytokines and trophic/cytotoxic effectors, proliferate, migrate and phagocytose.[1,2] Because of their perceived role as responders, it has been suggested that microglia can change the course of a disease but are rarely the cause of disease. This view is beginning to shift as more evidence supports the idea that although microglia are the surveillance cells of the central nervous system, they are also involved in physiologic processes such as neurogenesis, neurotransmission and maintenance of synapses.[1] Microglia are capable of inducing subtle alterations in the biochemistry of nearby neurons. For example, Coull and colleagues[3] demonstrated in a landmark study that, in vivo, brain-derived neurotrophic factor (BDNF) released from spinal cord microglia is responsible for reversing the γ-aminobutyric acid (GABA) currents in surrounding neurons, potentially providing a mechanism for the development of neuropathic pain. In addition to BDNF, microglial cytokines such as tumour necrosis factor-α and interleukin-1β (IL-1β) have also been shown to induce changes in neurotransmission, most notably the expression and phosphorylation of glutamate receptors.[4–6] Activated microglia are also known to secrete a large amount of glutamate via their glutamate transporters,[7] which could cause excitotoxicity in glutamatergic neurons but also more favourable changes such as reconstruction of synapses or synaptogenesis.

Regardless of whether the induced neuronal changes are major or subtle, it is without question that microglia have the potential to induce these changes in vivo and initiate the development of neuropsychiatric diseases. There are clear difficulties in studying the relative contribution of different cell types in an in vivo disease model; however, there is an array of cell culture studies showing that activated microglia treated with antidepressants or antipsychotics have a diminished activation profile, where the release of proinflammatory cytokines is downregulated.[8–12] One can deduce that the diminished release of microglial cytokines protects against the changes these cytokines would otherwise induce on nearby neurons. This in turn provides a plausible mechanism of action for antidepressants and antipsychotics, consequently implicating microglia in the pathology of several neuropsychiatric disorders.

Ultimately, whether or not neurons or glia are the initiators of the disease process may not be the critical issue, as the neuron–glia interaction is a 2-way feedback loop (Fig. 1). For example, although microglial cytokines can alter neurotransmission, neurotransmitters themselves can regulate microglial physiology, including their release of cytokines. Microglia express receptors for several neurotransmitters, including glutamate, adenosine 5′-triphosphate (ATP), GABA, dopamine and noradrenaline.[13] Activation of these receptors on microglia can regulate several microglial

Correspondence to: Dr. K.G. Todd, Neurochemical Research Unit, Department of Psychiatry and Centre for Neuroscience, University of Alberta, 12-127 Clinical Sciences Bldg., Edmonton AB T6G 2G3; fax 780 492-6841; kgtodd@ualberta.ca

J Psychiatry Neurosci 2009;34(3):173-4.

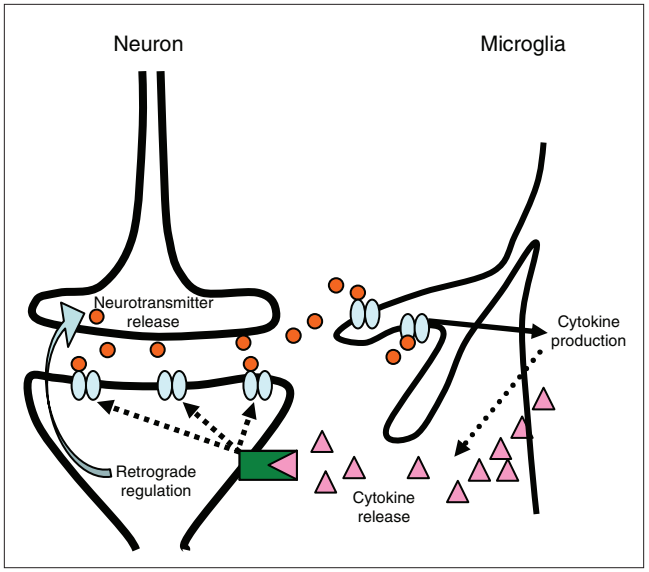

Fig. 1: Schematic of the 2-way feedback loop between neurons and microglia. The neurotransmitters (circles) released from the presynaptic terminal bind to the neurotransmitter receptors on both the postsynaptic membrane and nearby microglia. Strong activation of the receptors on microglia induces cytokine (triangles) production and release. The released cytokines bind to the cytokine receptors on neurons, which modulates the postsynaptic receptor expression and biochemistry and consequently affects the presynaptic transmitter release and overall neurotransmission.

effectors. For instance, high levels of ATP upregulate the release of microglial IL-1β, BDNF and nitric oxide and stimulate microglial chemotaxis.[14] The induced changes in microglial cytokines can then further modify neurotransmission, forming the 2-way feedback loop. Altered release of neurotransmitters is believed to be an underlying mechanism of several neuropsychiatric disorders. If this feedback loop is indeed involved, then the origin of the disease may be either neuronal or glial. Gaining a better understanding on the biology of microglia, and more importantly, the biology of neuron–microglia interactions, is crucial to elucidating the full pathological landscape of neuropsychiatric disorders.

A persisting challenge in the study of neuropsychiatric disorders is the lack of animal disease models that are widely believed to resemble the human disease condition. In diseases such as Alzheimer disease that have well-defined genetic models, the role of glia has received considerably more attention from investigators. For example, it has been shown that microglia can be both neuroprotective and neurotoxic in Alzheimer disease by degrading amyloid β plaques conferring neuroprotection or by increasing their release of proinflammatory cytokines such as IL-1β, which can promote neuronal degeneration. In diseases such as major depressive disorder that do not have the luxury of such genetic models, the understanding of glial biology is still limited. Cell culture studies examining the effects of antidepressants and antipsychotics on microglia may prove useful in elucidating the role of microglia in mood disorders and schizophrenia, but the transferability of cell culture data to in vivo conditions is always limited. Reliable and accepted in vivo models for neuropsychiatric disorders will enhance further study of the critical role played by glial cells in neuronal–glial interactions that may underlie the pathogenesis of neuropsychiatric diseases and the brain's response to their treatment.

Acknowledgements: The authors are funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council, The Heart and Stroke Foundation of Canada, and the George and Dorothy Davey Endowment.

Competing interests: None declared.

References

1. Hanisch UK, Kettenmann H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci* 2007;10:1387-94.
2. Lai AY, Todd KG. Microglia in cerebral ischemia: molecular actions and interactions. *Can J Physiol Pharmacol* 2006;84:49-59.
3. Coull JA, Beggs S, Boudreau D, et al. BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. *Nature* 2005;438:1017-21.
4. Beattie EC, Stellwagen D, Morishita W, et al. Control of synaptic strength by glial TNFalpha. *Science* 2002;295:2282-5.
5. Viviani B, Bartesaghi S, Gardoni F, et al. Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *J Neurosci* 2003; 23:8692-700.
6. Lai AY, Swayze RD, El-Husseini A, et al. Interleukin-1 beta modulates AMPA receptor expression and phosphorylation in hippocampal neurons. *J Neuroimmunol* 2006;175:97-106.
7. Takeuchi H, Jin S, Wang J, et al. Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. *J Biol Chem* 2006; 281:21362-8.
8. Kato T, Monji A, Hashioka S, et al. Risperidone significantly inhibits interferon-gamma-induced microglial activation in vitro. *Schizophr Res* 2007;92:108-15.
9. Bian Q, Kato T, Monji A, et al. The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-gamma. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:42-8.
10. Kato T, Mizoguchi Y, Monji A, et al. Inhibitory effects of aripiprazole on interferon-gamma-induced microglial activation via intracellular Ca^{2+} regulation in vitro. *J Neurochem* 2008;106:815-25.
11. Hwang J, Zheng LT, Ock J, et al. Inhibition of glial inflammatory activation and neurotoxicity by tricyclic antidepressants. *Neuropharmacology* 2008;55:826-34.
12. Zheng LT, Hwang J, Ock J, et al. The antipsychotic spiperone attenuates inflammatory response in cultured microglia via the reduction of proinflammatory cytokine expression and nitric oxide production. *J Neurochem* 2008;107:1225-35.
13. Pocock JM, Kettenmann H. Neurotransmitter receptors on microglia. *Trends Neurosci* 2007;30:527-35.
14. Inoue K. Purinergic systems in microglia. *Cell Mol Life Sci* 2008; 65:3074-80.