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DOES CHRONIC ANTIDEPRESSANT TREATMENT INCREASE EXTRACELLULAR SEROTONIN?

By Anne Milasincic Andrews

Many commonly prescribed antidepressants are hypothesized to relieve depressed mood and excessive anxiety by inhibiting the re-uptake of serotonin (and/or norepinephrine). Chronic transporter inhibition is widely believed to lead to homeostatic increases in extracellular neurotransmitter levels, which drive additional adaptive processes that have not been fully clarified, but together constitute the molecular and cellular mechanisms of current antidepressant therapy. By contrast, constitutive reductions in serotonin but not norepinephrine transporter function have been correlated with increased anxiety-related behavior in rodents, and similarly, heightened personality traits associated with negative emotionality in humans (Murphy et al., 2008; Ansorge et al., 2008). We recently reviewed the literature on serotonin system adaptive responses to chronic antidepressant administration and compared this with findings on constitutive loss of serotonin transporter (SERT) gene expression (Luellen et al., in press). Our goal was to discover whether differences in presynaptic neuroadaptation, resulting from constitutive versus adult onset reductions in SERT function, provide a basis for understanding divergent behavioral outcomes.

Partial genetic SERT deficiency in mice is associated with modest increases in extracellular serotonin, discernable by zero-net-flux microdialysis, whilst total absence of SERT results in substantial increases in extracellular serotonin (Mathews et al., 2004). By contrast, we examined over 50 microdialysis studies on chronic antidepressant administration and discovered that nearly half reported no change in dialysate serotonin levels, in contrast to increases in serotonin described in the remaining studies. We were unable to rectify these contradictory findings by considering drug or drug class, dose, route of administration, washout period, or brain region studied. Even when zero-net-flux microdialysis was employed to evaluate chronic antidepressant treatment, increases in extracellular serotonin were not detected in the hippocampus or frontal cortex following continuous delivery of therapeutic levels of paroxetine in mice (Gardier et al., 2003).

These largely discrepant findings on the effects of long-term antidepressant administration in experimental animals raise a number of issues. First, widely varying antidepressant administration protocols have been utilized across numerous studies, likely contributing to some of the discrepancies. Thus, it appears important to consider precisely drug doses and methods of delivery. Blood levels for individual antidepressants, doses, and routes of administration in experimental animals need to be determined to ensure that equivalent human therapeutic levels are achieved (Hirano et al., 2005). However, the ultimate test of an effective antidepressant administration paradigm lies in demonstrating that re-uptake is effectively blocked for at least a period of weeks. Secondly, these considerations apply to studies aimed at investigating the effects of antidepressants administered during critical developmental periods (Ansorge et al., 2008). Here, much additional work is needed to elucidate adaptive responses in the serotonergic system, as well as its postsynaptic targets, following inhibition of SERT function during pre- and postnatal periods, particularly regarding the persistence of neuroadaptive changes into adulthood. And thirdly, human therapeutic windows for most antidepressants, which are large, might reflect contributions from SERT gene variants that modulate transporter expression and function (Murphy et al., 2008). However, there might be other undiscovered factors at work in humans and animals influencing the ability of antidepressants to inhibit SERT effectively and, therefore, to raise extracellular levels of serotonin. In sum, the highly contradictory microdialysis literature on the effects of chronic antidepressant administration on extracellular serotonin levels highlights the need to establish neurochemically relevant dosing paradigms in experimental animals, but also to evolve strategies to evaluate drug effectiveness readily in individual patients.

Anne Milasincic Andrews’ interdisciplinary research focuses on serotonergic modulation of anxiety, stress, and learning and memory. She investigates the molecular bases of behavior and mechanisms of psychiatric drugs in vivo and in vitro using microdialysis, voltammetry, and immunocytochemistry, and is developing novel nanobiosensors. Prior to joining the Penn State faculty (1998-2003), Andrews was a fellow at the National Institute of Mental Health (1988-1998). She recently moved to the UCLA Department of Psychiatry and is also a member of the California NanoSystems Institute. ama@cnsi.ucla.edu


