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Editorial for the Special Issue: Monoamine Transporters in Health and Disease

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Editorial for the Special Issue: Monoamine Transporters in Health and Disease

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Monoamine neurotransmitters, including dopamine, norepinephrine, epinephrine, and serotonin, act in the central and peripheral nervous system to regulate behavioral processes including locomotion, motivation, arousal, anxiety, and mood, and physiological processes including temperature regulation, cardiovascular function, and intestinal motility. Dysregulation involving monoamine systems has been implicated in diverse pathological conditions, including but not limited to major depressive disorder, addiction, Parkinson's disease, schizophrenia, anxiety disorders, irritable bowel syndrome, and cardiovascular diseases. Thus, a large body of research has focused on understanding mechanisms involved in regulating monoaminergic transmission. Key among these mechanisms are monoamine transporters. Transporter-mediated processes determine the peak concentration, duration, and physical spread of released monoamines, as well as their intracellular disposition and metabolic fate. Not surprisingly, these transporters have been the subject of much research. Especially pertinent to

this issue is the role they play as key targets for drugs of abuse, including amphetamine and cocaine, as well as newly emerged psychoactive synthetic cathinones, also known as “bath salts” and “legal highs”, but also as the targets of pharmaceutical treatments for several neuropsychiatric disorders, including depression, anxiety and attention deficit hyperactivity disorder (ADHD). The most studied monoamine transporters in this regard have been the high-affinity, sodium-dependent transporters for dopamine, norepinephrine and serotonin (DAT, NET and SERT, respectively) and the vesicular monoamine transporters. However, in recent years a growing number of lower-affinity, higher-capacity (“uptake 2”) transporters, including the plasma membrane monoamine transporter (PMAT) and the organic cation transporters (OCT1-3), have emerged as important regulators of monoamine neurotransmission. In this special issue, we have assembled review articles and research papers from distinguished scientists in the field of monoamine transport that address regulation of transporter function; pathologies and therapeutic strategies involving monoamine transporters; drug effects on transporter function; tools for the study of transporter function; and atypical monoamine transporters.

Activity of monoamine transporters is regulated dynamically by post-translational modification and by trafficking within cells. In their reviews, Rastedt et al., and Foster and Vaughan, describe the role of phosphorylation and palmitoylation, respectively, in regulating cellular localization and activity of DAT, as well as the ability of amphetamine to stimulate DAT-mediated dopamine efflux. A research article by Sung et al. describes the cellular mechanisms underlying Ca^{2+}-dependent trafficking of NET.

Roles played by altered monoamine transporter function in pathological processes, and in therapeutic strategies are explored in four review articles. Butler et al. summarize studies examining regulation of DAT and dopaminergic neurotransmission by alpha-synuclein, a protein implicated in neurodegenerative and movement disorders. Margolis reviews evidence that alterations in SERT function may contribute to both brain and gut manifestations of autism spectrum disorders, and that developmental exposure to serotonin reuptake inhibitors may also lead to behavioral and gut abnormalities. Reciprocal regulation of DAT and insulin are reviewed by Nash, with an emphasis on potential mechanisms underlying metabolic side effects of antipsychotic treatment. Finally, Mikelman and colleagues describe modulation of DAT function by the estrogen receptor antagonist tamoxifen, and the potential of this drug as a treatment for amphetamine abuse.

Drug effects on transporter function are discussed in two articles. A research article by Shekar et al. describes the ability of the common bath salt constituent MDPV to drive reverse transport by DAT. Kudlacek and colleagues review studies examining effects of common adulterants added to cocaine, on DAT-, NET- and SERT-mediated transport.

Two articles describe development of new tools for the study of transporter localization and function. Karam et al. describe development and validation of two novel phospho-specific antibodies directed against the human DAT, phosphorylated at two distinct N-terminal serine residues. As reviewed in the contribution by Foster and Vaughan, phosphorylation of DAT has potent effects on its function, including effects on localization and activity. Thus, the availability of these tools will facilitate further elucidation of cellular mechanisms and functional consequences of DAT phosphorylation. The development of another new transporter-specific antibody, this one directed against VMAT2, is described in the contribution of Cliburn et al. This antibody is a welcome addition, as effective antibodies against VMAT2 have not been readily available. In addition to validating the antibody, Cliburn et al. demonstrate its utility in immunohistochemistry, immunoprecipitation and western blot.

Two articles describe research on what may be termed “atypical” monoamine transporters, members of the uptake 2 family of multi-specific monoamine transporters. A research article by Shirasaka and colleagues compares the functional properties of PMAT across human and rodent species. And finally, Gasser and Daws close with a commentary on studies examining contributions of organic cation transporters to regulation of monoaminergic signaling in brain.

In closing, we would like to take this opportunity to express our sincere gratitude to all authors and reviewers for their contributions to this special issue, and to our readers. Articles contained herein provide a timely perspective on our current understanding of monoamine transporter regulation, new tools for their study, and importantly, their role in health and disease. We hope that the contents of this issue help foster development of new ideas and research directions in the dynamic field of monoamine transporter research.