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REVIEW

THE SEROTONIN SYSTEM IN AUTISM SPECTRUM DISORDER: FROM BIOMARKER TO ANIMAL MODELS

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Abstract—Elevated whole-blood serotonin, or hyperserotonemia, was the first biomarker identified in autism spectrum disorder (ASD) and is present in more than 25% of affected children. The serotonin system is a logical candidate for involvement in ASD due to its pleiotropic role across multiple brain systems both dynamically and across development. Tantalizing clues connect this peripheral biomarker with changes in brain and behavior in ASD, but the contribution of the serotonin system to ASD pathophysiology remains incompletely understood. Studies of whole-blood serotonin levels in ASD and in a large founder population indicate greater heritability than for the disorder itself and suggest an association with recurrence risk. Emerging data from both neuroimaging and postmortem samples also indicate changes in the brain serotonin system in ASD. Genetic linkage and association studies of both whole-blood serotonin levels and of ASD risk point to the chromosomal region containing the serotonin transporter (SERT) gene in males but not in females. In ASD families with evidence of linkage to this region, multiple rare SERT amino acid variants lead to a convergent increase in serotonin uptake in cell models. A knock-in mouse model of one of these variants, SERT Gly56Ala, recapitulates the hyperserotonemia biomarker and shows increased brain serotonin clearance, increased serotonin receptor sensitivity, and altered social, communication, and repetitive behaviors. Data from other rodent models also suggest an important role for the serotonin system in social behavior, in cognitive flexibility, and in sensory development. Recent work indicates that reciprocal interactions between serotonin and other systems, such as oxytocin (OT), may be particularly important for social behavior. Collectively, these data point to the serotonin system as a prime candidate for treatment development in a subgroup of children defined by a robust, heritable biomarker.

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Key words: genetic, monoamine, reuptake, platelet, neurodevelopment, multisensory.

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INTRODUCTION

Findings from multiple domains of research have implicated the serotonin system in autism spectrum disorder (ASD). Initial findings more than 50 years ago identified elevated whole-blood serotonin levels, termed hyperserotonemia, in a subset of children with autism. Since then, work on the serotonin system in ASD has extended intermittently as new tools have become

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Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; ASD, autism spectrum disorder; *ITGB3*, integrin β3 subunit gene; MAOA, mitochondrial bound protein monoamine oxidase A; MAPK, mitogen-activated protein kinase; MDMA, 3,4-methylenedioxymethamphetamine; NAS, N-acetylserotonin; OCD, obsessive–compulsive disorder; OT, oxytocin; PKG, protein kinase G; SERT, serotonin transporter; *SLC6A4*, serotonin transporter gene; SSRIs, serotonin reuptake inhibitors; TPH, tryptophan hydroxylase.

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available, from pharmacology to genetics to neuroimaging. Emerging findings, driven largely by advances in mouse models, point to the importance of serotonin for social function, repetitive behavior, and sensory development. With the increasing recognition of heterogeneity in ASD, biological markers will play an important role in identifying subsets of children who are more likely to share common risk or benefit from the same treatments. The combination of a robust biomarker with a rich understanding of serotonin neurobiology suggests that the serotonin system is particularly ripe for treatment development in a subset of children with ASD.

BRIEF OVERVIEW OF THE SEROTONIN SYSTEM

For millions of years, serotonin (5-hydroxytryptamine, 5-HT) has existed as a signaling molecule across phylogeny (Hay-Schmidt, 2000). It is produced from the essential amino acid, tryptophan, via a two-step synthetic pathway. In the first step, tryptophan is converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase (TPH) (Fig. 1). There are two isoforms of tryptophan hydroxylase, TPH1 and TPH2, which are primarily responsible for 5-HT synthesis in the periphery and central nervous system (CNS), respectively (Lovenberg et al., 1967; Walther et al., 2003). In the final step, the intermediate product, 5-HTP, is converted to 5-HT by aromatic acid decarboxylase (AADC). Degradation of 5-HT primarily occurs by the mitochondrial bound protein monoamine oxidase A (MAOA), leading to the production of the metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Importantly, serotonin also serves as an intermediate substrate for melatonin synthesis.

Though more recognized for its role as a neurotransmitter, the vast majority of 5-HT produced in the body is located in the periphery. Specifically, enterochromaffin cells that line the lumen of the gastrointestinal tract are the primary source of peripheral 5-HT, which is then taken up by platelets as they pass through the enteric circulation (Anderson

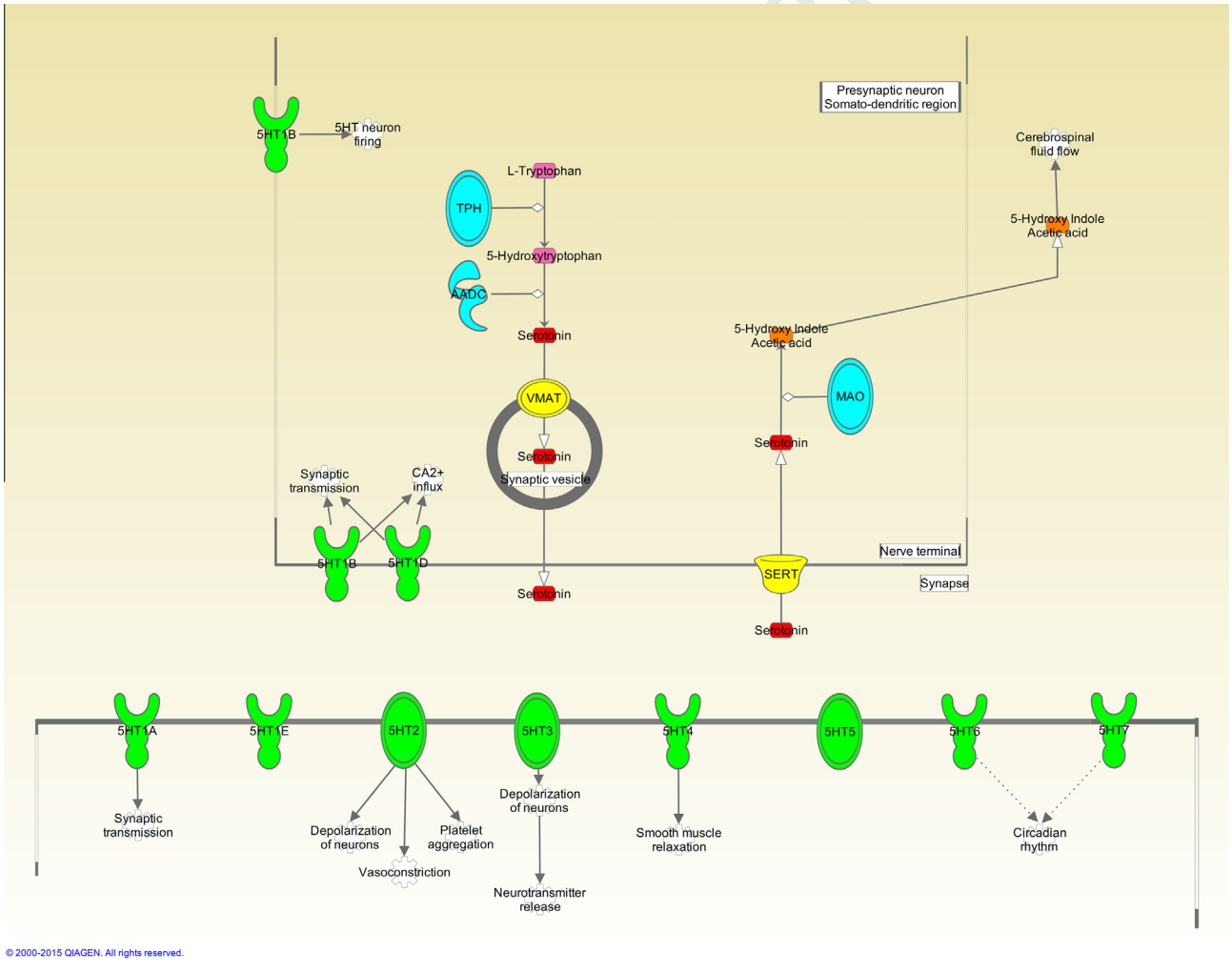

Fig. 1. Overview of the serotonin system. This cartoon depicts the serotonin synthesis, release, reuptake, and degradation, as well as the canonical roles of a subset of serotonin receptors. TPH = tryptophan hydroxylase. AADC = aromatic acid decarboxylase. VMAT = vesicular monoamine transporter. SERT = serotonin transporter. MAO = monoamine oxidase. 5HT1–7 = serotonin receptor subgroups (oval shape) and individual receptors (goblet shape). Figure created using Ingenuity Pathway Analysis (Qiagen, Valencia, CA).

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