Neurochemistry International 66 (2014) 15–26

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Review

Decoding the contribution of dopaminergic genes and pathways to autism spectrum disorder (ASD)

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ARTICLE INFO

Article history:
Received 20 October 2013
Received in revised form 24 December 2013
Accepted 6 January 2014
Available online 9 January 2014

Keywords:
Autism
Dopaminergic system
Molecular pathways
Translational research
Genetics

ABSTRACT

Autism spectrum disorder (ASD) is a debilitating brain illness causing social deficits, delayed development and repetitive behaviors. ASD is a heritable neurodevelopmental disorder with poorly understood and complex etiology. The central dopaminergic system is strongly implicated in ASD pathogenesis. Genes encoding various elements of this system (including dopamine receptors, the dopamine transporter or enzymes of synthesis and catabolism) have been linked to ASD. Here, we comprehensively evaluate known molecular interactors of dopaminergic genes, and identify their potential molecular partners within up/down-steam signaling pathways associated with dopamine. These *in silico* analyses allowed us to construct a map of molecular pathways, regulated by dopamine and involved in ASD. Clustering these pathways reveals groups of genes associated with dopamine metabolism, encoding proteins that control dopamine neurotransmission, cytoskeletal processes, synaptic release, Ca^{2+} signaling, as well as the adenosine, glutamatergic and gamma-aminobutyric systems. Overall, our analyses emphasize the important role of the dopaminergic system in ASD, and implicate several cellular signaling processes in its pathogenesis.

Contents

1. Introduction

Autism is a complex 'system' disorder that involves the interactions among multiple organs, including the brain, immune, gastrointestinal and other systems (Geschwind, 2008; Kesli et al., 2014; Matson et al., 2012). Recognized for its 'spectrum' nature, autism spectrum disorder (ASD) is a serious neurodevelopmental illness that affects approximately 1–2% of the general population, and has a significant societal and mental health impact (Evans, 2013; Mayes et al., 2011). ASD is characterized by several 'core' syndromes (including social/communication deficits and repetitive behavior) with developmental pathogenic trajectory (Table 1). ASD is frequently comorbid with other brain disorders, such as anxiety, depression and attention deficit hyperactivity disorder (ADHD). Furthermore, ASD is a complex polygenic disorder, with

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http://dx.doi.org/10.1016/j.neuint.2014.01.002

nearly 550 human ASD-related genes currently listed in the Simons Foundation Autism Research Initiative (SFARI) Gene database (https://gene.sfari.org). Unique because of its very high (~90%) heritability, ASD represents one of the most heritable brain disorders (Crawley, 2012; Edvardson et al., 2013). Therefore, understanding the genetic determinants and associated molecular pathways of ASD may enable its better treatment and prevention (Edvardson et al., 2013; Geschwind, 2008; Kesli et al., 2014; Matson et al., 2012).

The central dopaminergic system has been strongly implicated in ASD (Hamilton et al., 2013; Hosenbocus and Chahal, 2012; Robinson et al., 2001; Staal et al., 2012). For example, pharmacological modulation of central dopamine is involved in clinical ASD (Diler et al., 2002; Hosenbocus and Chahal, 2012). Dopaminergic genes encoding dopamine transporter (DAT) (Hamilton et al., 2013), several dopamine receptors (Hettinger et al., 2012; Qian et al., 2013; Reiersen and Todorov, 2011), as well as enzymes of dopamine synthesis (DOPA decarboxylase, DDC) and catabolism (catechol-O-methyltransferase, COMT and monoamine oxidases MAO-A and -B), have also been linked to ASD (Table 2).

Complementing human data, animal (experimental) models of ASD are a valuable tool in uncovering its pathogenesis. For example, several popular genetic mouse models display social, motor and cognitive phenotypes which can be used for phenotyping rodent ASD-like behavior (Brodkin, 2007; Crawley, 2012; Fairless et al., 2013; Kas et al., 2013; McFarlane et al., 2008; Moy et al., 2008; Ryan et al., 2010; Silverman et al., 2012). Paralleling clinical ASD, animal ASD-like phenotypes typically include social deficits (e.g., lack of preference for social novelty, reduced social interactions, and vocalizations and social recognition), cognitive deficits (e.g., impaired learning and memory), repetitive behaviors (e.g., self-grooming, and stereotyped circling behavior) and behavioral perseverations (e.g., deficits in reversal learning in Morris water maze and T-maze); see (Crawley, 2012; Kas et al., 2013) for a comprehensive critical review. Reflecting this rapidly expanding field, the comprehensive Mouse Genome Informatics database (MGI, http://www.informatics.jax.org) and SFARI Gene database currently list almost 500 animal models and 160 mouse genes potentially relevant to ASD-like phenotype. Applying these bioinformatics tools, it now becomes possible to assess human ASD-related genes in relation to those identified in mice, collectively generating important mechanistic insights into the neurobiology of this disorder.

2. Identifying dopamine-associated genes potentially relevant to ASD

Despite recent progress in dissecting the neural underpinnings of ASD (Kéïta et al., 2011; Kujala et al., 2013), its genetic determinants remain poorly understood (Geschwind, 2008). While untangling the genetic determinants of ASD presents a challenge, bioinformatics-driven approaches may improve our understanding of its pathogenesis, also identifying new important targets (Sakai et al., 2011). To achieve this goal, we attempted to analyze human and mouse dopamine-related genes (including genes of dopamine receptors, transporters and enzymes) *in silico*, and assess their role in ASD. We also aimed to build signaling networks (associated with molecular partners of these dopaminergic genes' protein products), and identify potential key interactors likely to contribute to ASD pathogenesis. Finally, clustering these molecular networks based on their signaling role allowed us to identify critical molecular pathways associated with the dopaminergic regulation of ASD.

The overall rationale of our analyses is briefly summarized in Fig. 1 (also see Fig. 2 for a general overview of dopamine signaling, directly related to the logic of our approach). The publicly available SFARI Gene database was first used to select human and mouse dopaminergic ASD-related genes (assessed October–November 2013). Human genes (and their respective mouse orthologs) utilized in our analyses included genes of dopamine receptors (DRD1, DRD2, DRD3, DRD4, DRD5), dopamine-synthesizing enzyme DDC, dopamine transporter (DAT) and dopamine-catabolizing enzymes COMT and MAO (Fig. 2). The Search Tool for the Retrieval of Interacting Genes/Protein online database (STRING; http://string-db.org/) was further used to build molecular networks based on known molecular interactions between the protein products of identified genes. The medium confidence interval (0.40) and 'minimal number of interactors' <50 were selected to search for molecular networks for the selected dopaminergic genes. We employed a conservative approach to selecting molecular interactors, using 'experimental data' as the search criterion (i.e., not assessing indirect evidence, such as text mining, co-occurrence or co-expression data). The STRING database search was separately performed for human (*Homo sapiens*) and mouse (*Mus musculus*) genes. Once the interactors for each dopaminergic gene were identified (Table 2), they were next compared with the mouse and human 'ASD genes' from the SFARI database, in order to identify interactor genes (from dopaminergic networks) also associated with ASD. In addition, a comprehensive literature search using the Pubmed database (http://www.ncbi.nlm.nih.gov/pubmed, assessed October–November 2013) was performed using "autism", "autistic" and "ASD" as search terms, in order to examine additional evidence of association of various identified genes in ASD pathogenesis (Tables 2 and 3). Table 2 summarizes genes from dopaminergic pathways which appear to be associated with ASD, based on our analyses. Table 3 contains detailed information on these genes, including their protein products, cellular location and function. Fig. 3 provides a visualized map-like summary of molecular mechanisms associated with the key ASD-associated genes listed in Table 2, collectively illustrating the complex landscape of dopaminergic pathways implicated in ASD pathogenesis (see detailed discussion further).

Table 1
Summary of diagnostic criteria for Autism Spectrum Disorder (ASD), according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) of the American Psychiatric Association (2013).

A. Social deficits

Persistent deficits in social communication and interaction, such as (i) deficits in social-emotional reciprocity and social approach, failure to initiate/respond to interactions; (ii) deficits in verbal/nonverbal communication, poor eye contact and body language, deficits in understanding/use of gestures; a lack of facial expressions; and (iii) deficits in developing and understanding relationships, adjusting behavior to various social contexts, making friends

B. Behavioral and cognitive perseverations

Restricted, repetitive patterns of behavior, interests or activities, manifested by at least two of the following: (i) stereotyped/repetitive motor movements, use of objects or speech; (ii) insistence on sameness, routines, ritualized patterns in verbal/nonverbal behavior; (iii) highly restricted interests abnormal in intensity or focus; and (iv) hyper/hyporeactivity to sensory input or sensory aspects of the environment

C. Symptomatic trajectory

Symptoms must be present during early development (but may not fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life) and cause clinically significant impairment in social, occupational, or other areas of functioning