Drug Discovery Today • Volume 00, Number 00 • December 2013 PERSPECTIVE

feature

The promising trajectory of autism therapeutics discovery

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Pharmacological interventions for neurodevelopmental disorders are increasingly tractable. Autism is a neurodevelopmental disorder that affects approximately 1% of the population. Currently, the standard of care is early behavioral therapy. No approved medical treatments for the diagnostic symptoms are available. Strong evidence for genetic causes of autism implicates proteins that mediate synaptic transmission and structure. Mouse models with targeted mutations in these synaptic genes display behavioral symptoms relevant to the social communication abnormalities and repetitive behaviors that define autism spectrum disorder (ASD), along with biological abnormalities in synaptic physiology and morphology. As we discuss here, promising pharmacological targets, emerging from the mouse model studies, are now being pursued in early clinical trials. Thus, a high-prevalence disorder that was previously considered to be medically untreatable is now moving into the therapeutic arena.

Neurodevelopmental disorders were historically viewed as intractable to pharmacological interventions. The assumption was that abnormalities in brain development began prenatally, and were irreversible by the age of diagnosis. Recent discoveries implicate multiple genes in the causes of autism and related neurodevelopmental disorders. Many of these genes encode synaptic proteins that regulate the formation, maturation and strengthening of synaptic connections between neurons. Several genes encode neurotransmitter receptors that mediate excitatory and inhibitory synaptic transmission. Given that synaptic processes are ongoing in real time, synaptic transmission can be modified at any age and disease stage by available or novel pharmacological agents. New strategies focused on synaptic signaling targets indicate that compounds acting through signaling mechanisms could lead to efficacious pharmacotherapies for the diagnostic symptoms of autism.

Genetic advances

Single gene mutations are responsible for many neurodevelopmental disorders [1]. Fragile X syndrome, the major genetic cause of intellectual impairment, is produced by an expansion mutation in Fragile X mental retardation 1 (*FMR1*). The mutation causes loss of function of the translational repressor protein, Fmrp, the Fragile X mental retardation protein. Rett syndrome is caused by a mutation in the gene encoding methyl-CpG-binding protein 2 (*MECP2*), which binds to methylated DNA and represses transcription. Tuberous sclerosis is caused by a mutation in a tumor suppressor gene, tuberous sclerosis (*TSC*), which regulates the mammalian target of rapamycin (mTOR) signaling. Many other examples of monogenic neurodevelopmental disorders with intellectual impairment are revealing biochemical mechanisms that appear to be amenable to therapeutic interventions derived from known mechanisms of action [2,3]. For example, increasing knowledge about the downstream proteins upregulated by the *FMR1* mutation has led to the first clinical trials for Fragile X syndrome [4].

Autism is a particularly intriguing neurodevelopmental disorder, which is diagnosed uniquely and is often comorbid with other neurodevelopmental disorders. Autism is usually diagnosed when patients are 2–5 years old, based solely on two categories of behavioral symptoms: (i) persistent deficits in social interactions and social communication; and (ii) stereotyped and repetitive behaviors, with restricted interests and inflexibility [5]. Formally termed autism spectrum disorder (ASD), the syndrome encompasses considerable variability

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Please cite this article in press as: J.L. Silverman,, The promising trajectory of autism therapeutics discovery, Drug Discov Today (2014), http://dx.doi.org/10.1016/j.drudis.2013.12.007

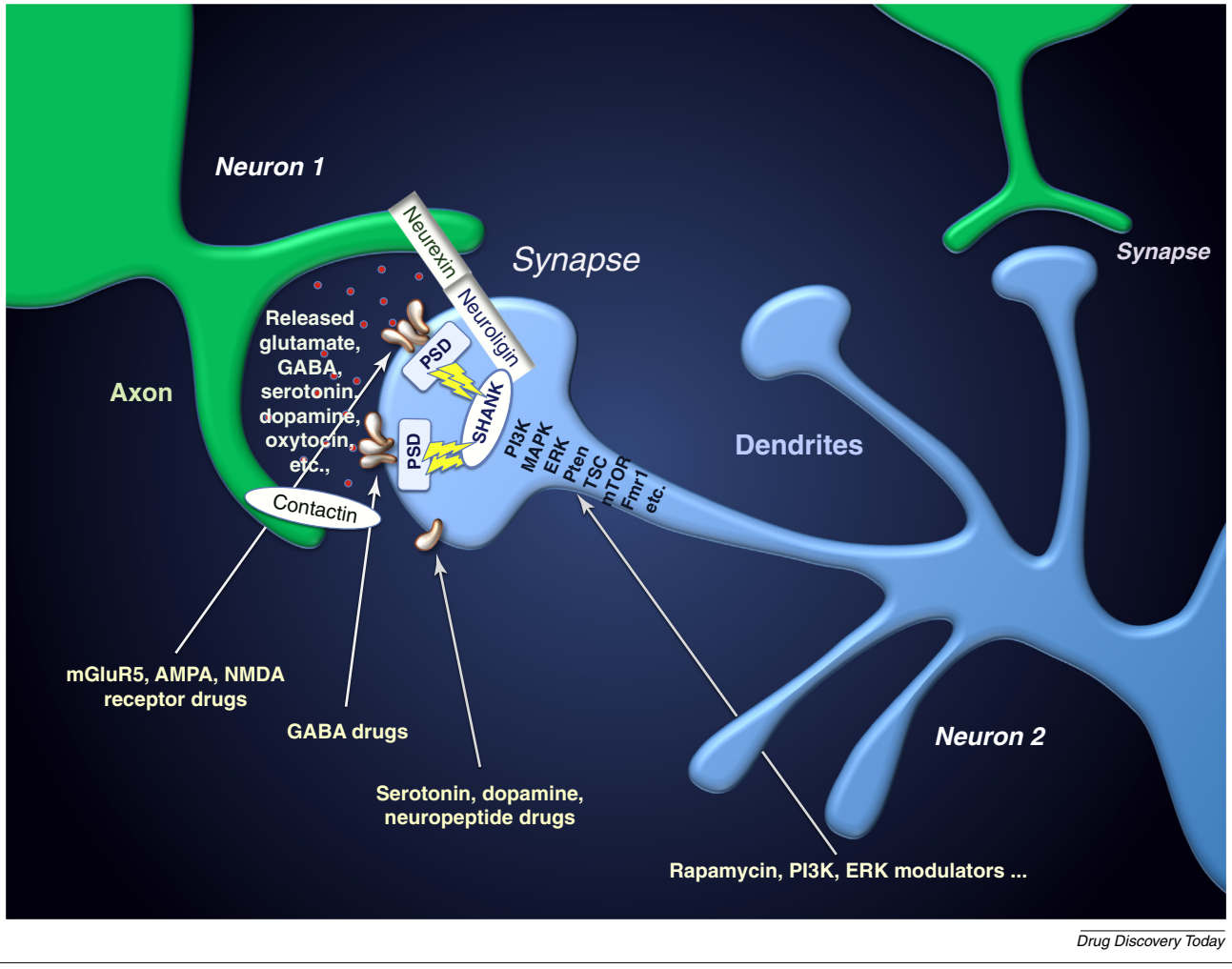

FIGURE 1

Synaptic genes predict pharmacological targets for therapeutic interventions in autism. The synapse comprises the axon projecting from neuron 1, the dendrites extending from neuron 2 and the small spatial gap between axon and dendrite. Synapses form, mature and strengthen in response to activity-driven stimulation. Presynaptic neurexins, cadherins, contactin-associated proteins and other cell adhesion molecules bind to postsynaptic cell adhesion molecules, such as neuroligins 1, 2, 3 and 4, to anchor the synapse. Neurotransmitters, such as glutamate, gamma-aminobutyric acid (GABA), serotonin, oxytocin and dopamine, are released from the axon terminal to cross the spatial gap. Receptors on the dendritic extension, such as the glutamatergic *N*-methyl-*D*-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and mGluR5, bind the neurotransmitter, initiating a cascade of postsynaptic events. Postsynaptic densities (PSD) thicken with newly synthesized proteins, forming a cytoarchitectural scaffold of proteins including SH3 and multiple ankyrin repeat domains (Shank) 1, 2 and 3. Downstream signaling molecules, such as phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinases (MAPK), extracellular signal-regulated kinases (ERK), phosphatase and tensin homolog (Pten), tuberous sclerosis (TSC) and mammalian target of rapamycin (mTOR), initiate biochemical events in neuron 2, to convert the activity-driven neurotransmitter signals emitted by neuron 1 into action events within neuron 2. Fragile X mental retardation protein (Fmr1) is a negative regulator of translation, inhibiting the synthesis of multiple downstream signaling proteins. Mutations in the genes encoding many of these synaptic elements in patients with autism and related neurodevelopmental disorders suggest therapeutics targets with known mechanisms of action. Existing compounds acting at these targets, including neurotransmitter receptors, allosteric receptor modulators, signaling elements and translation modifiers, offer repurposing opportunities to discover effective treatments for autism spectrum disorder.

in the expression and severity of symptoms. Commonly associated symptoms include seizures, anxiety, intellectual impairment, attentional abnormalities, hyperactivity, aberrant reactivity to sensory stimuli, gastrointestinal disturbances and sleep disruption. The current standard of care is early intensive behavioral interventions. One class of drugs has been approved for autism by the US Food and Drug Administration (FDA), the antipsychotics risperidone and aripiprazole [6–8]. These reportedly reduce 'irritability' (i.e. aggression, temper tantrums and self-injury), but do not generally modify the primary diagnostic symptoms or disease progression.

Although many environmental causes of autism have been proposed, the largest body of evidence invokes genetic factors [1,9]. Approximately 25% of autism cases are attributable to a genetic cause, either an inherited or a *de novo* mutation, including comorbidities with other syndromes, such as Fragile X and tuberous sclerosis. The search for candidate genes was spurred by consistent reports of a boy:girl ratio of 4:1 or higher, and a striking concordance between monozygotic twins, as high as 90% in some studies. In contrast, concordance for ASD between fraternal twins and siblings is 10–30%, and prevalence in the general population is approximately 1%.

Genome-wide association studies rapidly advanced the autism research field with the discovery of several key genetic mutations in patients with autism [10,11]. Taken together, the genetic evidence paints an elegant portrait of the neuronal synapse [12], as illustrated in Fig. 1. Mutations in SH3 and multiple ankyrin repeat

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