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REVIEW

Serotonin in psychiatry: in vitro disease modeling using patient-derived neurons

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Abstract Several lines of evidence implicate serotonin in the etiology of multiple psychiatric disorders, especially mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD). Much of our current understanding of biological mechanisms underlying serotonergic alterations in mood disorders comes from animal studies. Innovation in induced pluripotent stem cell and transdifferentiation technologies for deriving neurons from adult humans has enabled the study of disease-relevant cellular phenotypes in vitro. In this context, human serotonergic neurons can now be generated using three recently published methodologies. In this mini-review, we broadly discuss evidence linking altered serotonergic neurotransmission in MDD and BD and focus on recently published methods for generating human serotonergic neurons in vitro.

Introduction

Serotonin or 5-hydroxytryptamine (5-HT) is an ancient and evolutionarily conserved neurotransmitter known to be involved in a broad range of physiological processes and behaviors such as cardiovascular regulation, pain sensitivity, feeding, reproductive behavior, cognition, impulsivity, aggression and mood. A large body of clinical and pre-clinical research has implicated serotonin in the pathophysiology of multiple psychiatric disorders and the serotonergic neurotransmitter system is a target of several classes of therapeutic psychiatric drugs as well as other psychotropic drugs. Despite decades of research, our understanding of the precise roles of serotonin in psychiatric disorders and in the mechanism of action of therapeutic drugs remains largely incomplete (Albert and Benkelfat 2013; Albert et al. 2012; Liu and Deneris 2011). This may be partly due to the heterogeneous nature of psychiatric disorders and is further compounded by the complexity of the serotonergic neurotransmitter system. A large part of our current understanding of the cellular and molecular mechanisms linking serotonergic alterations to psychiatric disorders comes from behavioral observations in transgenic animal models, which sometimes poorly recapitulate the genetics and the psychiatric symptomatology observed in patients (Krishnan and Nestler 2010).

Utilizing patient-derived cells for generating disease-relevant cell types offers a new approach for investigating the genetic and cellular mechanisms that may play fundamental roles in psychiatric disorders (Soliman et al. 2017). Proof-of-concept studies have revealed unexpected neural phenotypes in studying schizophrenia, autism spectrum disorders, bipolar disorder, William's syndrome and Timothy syndrome (Brennand et al. 2011; Chailangkarn et al. 2016; Marchetto et al. 2017; Mertens et al. 2015; Pasca et al. 2011; Stern et al. 2017; Tian et al. 2014; Wen et al. 2014; Yi et al. 2016). Since the advent of induced pluripotent stem cell (iPSC) and transdifferentiation technologies, several research groups have focused their efforts on developing methods for generating disease-relevant neural subtypes in vitro (Parr et al. 2017). We and two other groups have developed protocols for generating human serotonergic neurons in vitro (Vadodaria et al. 2016a). The field of serotonin and psychiatry is large, with

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diverse associations being drawn with major depressive disorder (MDD) and bipolar disorder (BD), schizophrenia and autism spectrum disorders. In this article, we first highlight key lines of evidence implicating serotonergic alterations in mood disorders, focusing our discussion of clinical serotonergic alterations to MDD and BD and then discuss methods for generating human serotonergic neurons in vitro in the context of their utility for disease modeling.

Serotonergic alterations in MDD

Characterized by the presence of an array of persistent symptoms including low mood, anhedonia, suicidal thoughts, lack of concentration, appetite/weight fluctuations and sleep disturbances, MDD is the most prevalent psychiatric disorder in the United States with over 16 million adults suffering in a given year (NIMH data 1 n.d.). MDD has long been linked, at least in part, to serotonergic alterations. Some of the first evidence leading to what came to be known as the "monoamine hypothesis of depression" came from anecdotal evidence and from pharmacological studies that depleted or increased the concentration of brain monoamines (Charney 1998; Mosienko et al. 2015). Treatment with reserpine, an antihypertensive and vesicular monoamine transporter inhibitor, precipitated depressive symptoms (Shore et al. 1957). Similarly, dietary depletion of tryptophan, an essential amino acid and serotonin precursor, precipitated depressive symptoms in a subset of patients with a prior history of depressive illness (Homan et al. 2015). Further, first generation antidepressant drugs such as monoamine oxidase inhibitors and tricyclic antidepressants were found to increase brain neurotransmitter levels and second generation antidepressants such as selective serotonin reuptake inhibitors (SSRIs) specifically increased serotonin levels, supporting the idea that reduced monoamines, especially serotonin, might play a modulatory role in the pathophysiology of MDD (Heninger et al. 1996). However, despite an increase in brain serotonin levels following acute antidepressant administration, weeks of treatment are required before therapeutic effects are seen. This fact alone indicates that the picture of MDD pathology is more complex than that painted by the simplistic "monoamine hypothesis" of depression (Krishnan and Nestler 2008). Atypical antidepressants, on the other hand, do not necessarily block the reuptake of serotonin or other monoamines but have other targets including serotonergic receptors. Many atypical antidepressants, including mirtazapine, nefazodone, trazodone and vortioxetine, have high binding affinities for serotonergic families of receptors, notably the 5-HT1, 5-HT2, 5-HT3 and 5-HT7 receptors. 5-HT receptors are expressed in several brain regions targeted by serotonergic neurons and also in serotonergic neurons

themselves, suggesting that atypical antidepressants may mediate their therapeutic effects by modulating serotonergic neurotransmission in target brain regions, as well as in the raphe itself (Artigas 2013). Although inconsistent in the directionality of change, sets of positron emission tomography (PET) imaging studies have shown alterations in 5-HT1A receptors, 5-HT2A receptors and the serotonin transporter levels in the hippocampus, amygdala, midbrain, brainstem and multiple cortical regions (Fujita et al. 2000; Lin et al. 2014). A set of studies on small cohorts of unmedicated MDD patients showed decreased 5-HT1A receptor binding in several brain regions, including the mesiotemporal cortex, dorsolateral prefrontal cortex, amygdala, hippocampus and decreased 5-HT2A receptor binding in the temporal, parietal, prefrontal and cingulate cortex of patients (Bhagwagar et al. 2004; Hirvonen et al. 2008). Another set of imaging studies showed lower serotonin transporter binding in the brainstem, midbrain, and amygdala and higher serotonin transporter binding in the thalamus, insular cortex and striatum (Lin et al. 2014).

Although a study of monozygotic twins with MDD showed only modest concordance (~40%), genetic epidemiological studies and their meta-analyses suggest that the familial nature of major depression has a genetic basis (Flint et al. 2008). Genome-wide association studies have implicated the serotonin transporter gene (5-HTT) and serotonergic receptor genes (5-HT1, 5-HT2, 5-HT3) in MDD. One study showed that offspring with high familial risk of depression were nearly four times more likely to be homozygous for the short allele at 5-HTT promoter-linked polymorphism (5HTTLPR) (Talati et al. 2015). Interestingly, the short allele at the 5-HTTLPR was also found to be associated with increased cortical thickness in individuals with high familial risk for depression as found in an MRI study (Bansal et al. 2016). Another study of more than 100 depressed patients revealed an association of the short allele of 5HTTLPR with dysphoria and an association of the 5-HT2A receptor (1438G/A) polymorphism with vegetative symptoms in MDD, suggesting that specific polymorphisms may be associated with discrete symptom clusters in MDD (Kamata et al. 2011). However, MDD genetics have been notoriously difficult to dissect and a lack of replication across different patient cohorts highlights the heterogeneity of the disorder and its divergent genetic architecture (Flint and Kendler 2014; Major Depressive Disorder Working Group of the Psychiatric GC et al. 2013). Nevertheless, meta-analysis studies using data from large and varied patient cohorts suggest that overall, MDD genetic studies maybe statistically underpowered (Flint and Kendler 2014). Future studies would certainly benefit from patient stratification based on additional criteria (Ostergaard et al. 2015); for instance, drug response profiles (Ji et al. 2013), age (Power, et al. 2017), or fMRI-based neurophysiological subtypes (Drysdale et al. 2017) and higher numbers of patient within subgroups (Bigdeli et al. 2017; Hek et al. 2013).

Although BD, formerly known as manic depressive illness, diagnostically frequently overlaps with depression, BD has been found to be highly heritable with a number of genomic risk loci shared with schizophrenia and autism spectrum disorders (Panchision 2016). In the next section, we discuss genetic data and pharmacological and imaging studies that link serotonergic alterations with BD.

Serotonergic alterations in BD

Affecting 2–3% of the population, BD is characterized by distinct changes in mood states, energy and activity levels. Individuals with BD experience periods of mild/severe depressed mood states and periods of high energy and elation known as manic episodes (NIMH data 2 n.d.). Medications usually used to treat BD include mood stabilizers, atypical antipsychotics and antidepressants. Lithium, which is one of the most effective mood stabilizers used in BD, has been shown to regulate serotonin receptors (5-HT1A and 5-HT2A) in pre-clinical studies. Short-term lithium treatment in rodents has been shown to enhance 5-HT1A receptor responsiveness specifically at postsynaptic sites, whereas long-term treatment with lithium downregulates postsynaptic serotonin receptors, in part by modulating presynaptic serotonergic nerve terminals (Blier et al. 1987; Hotta et al. 1986). Interestingly, in patients concurrently taking serotonergic medications such as antidepressants, lithium can potentially precipitate 'serotonin syndrome' arising from excessive serotonin in the body, suggesting that lithium may be activating the serotonergic system. On the other hand, evidence suggests that treatment with antidepressants alone may aggravate symptoms such as anxiety and even mania and therefore may need to be combined with antimanic agents (Cannon et al. 2007). A majority of atypical antipsychotic drugs prescribed for BD, such as quetiapine, olanzapine and lurasidone, target multiple pathways but also display high affinities for multiple serotonergic receptors, including the 5-HT1A, 5-HT2A-C, 5-HT6 and 5-HT7 receptors (Fountoulakis et al. 2015; Mendonca Junior et al. 2015). However, given the dual mood states characteristic of BD, it is plausible that serotonergic alterations following pharmacological intervention may be acting to alleviate depressive states. PET imaging studies have shown increased 5-HT1A receptor levels in the raphe, hippocampus, dorsolateral prefrontal cortex and amygdala of BD patients (Sullivan et al. 2009) and decreased 5-HT1A receptor levels in the anterior cingular cortex, anterior insula and mesiotemporal cortices (Drevets et al. 2007; Nugent et al. 2013), while others showed decreased serotonin transporter binding in the midbrain, amygdala, hippocampus, thalamus, putamen and anterior cingulate cortex and increased serotonin transporter binding in the insula and striatum of BD patients. Genetic studies in large populations and their meta-analyses

(Cho et al. 2005) revealed an association with two polymorphisms for the serotonin transporter (5-HTTLPR and VNTR) (Kishi et al. 2011). Large-scale meta-analysis studies with approximately 1000 BD patients, with a haplotype-wise analysis, found an association of HTR1A rs6295 polymorphism and BD and discovered the 5-HT1A receptor to be a susceptibility gene for mood disorders (Kishi et al. 2011; Kishi et al. 2013) These findings may relate to increased DNA methylation found at the 5-HT1A receptor promoter region (Carrard et al. 2011). It is noteworthy that the 5-HT1A receptor is a heteroreceptor that is highly expressed in the raphe neurons and responsible for feedback auto-inhibition in serotonergic neurons.

While multiple links clearly exist between serotonergic alterations and mood disorders, the complex interplay between genetic and cellular mechanisms underlying MDD and BD remains poorly understood. It is also important to note that there exist multiple hypotheses for neural mechanisms underlying MDD and BD, including altered glutamatergic and GABAergic neurotransmission, with imbalances between these systems contributing to the pathophysiology of MDD (Gerhard et al. 2016; Lener et al. 2017). Two recent studies using BD patient iPSC-derived neurons revealed a hyperexcitability phenotype of Prox1 expressing hippocampal neurons, emphasizing the relevance of using human iPSC-based models (Mertens et al. 2015; Stern et al. 2017). Future studies utilizing patient-derived serotonergic neurons may yield novel insights into the role of serotonergic neurotransmission in these disorders. In the next section, we provide an overview of the developmental program and transcriptional cascades driving serotonergic fate specification in vivo and how they have been harnessed for deriving serotonergic neurons from human fibroblasts and iPSCs.

Generating human serotonergic neurons in vitro

Following the publication of the first methodologies for generating neurons from human iPSCs, several groups have published methods for generating and enriching specific neural subtypes in vitro for comparing disease-relevant cellular phenotypes from patient-derived cells (Parr et al. 2017). There are now methods available for generating several neural subtypes. Over the last year, we, along with two other groups, have developed methodologies for generating serotonergic neurons in vitro from human fibroblasts and iPSCs. Our group and Jian Feng's group overexpressed sets of serotonergic transcription factors for transdifferentiating human fibroblasts into serotonergic neurons (Vadodaria et al. 2016b; Xu et al. 2016) and Su-Chun Zhang's group utilized combinations of growth factors and developmental signaling molecules to differentiate human iPSCs into raphe-like serotonergic neurons (Lu et al. 2016). Remarkably, each method generated 25–50%

serotonergic neurons that displayed key functional properties. In the next section, we discuss key aspects of raphe development in the context of utilizing them in vitro.

Specification of serotonergic neurons within the developing raphe nuclei is directed by a combination of developmental signaling molecules. Broadly, Sonic hedgehog (Shh) released by the notochord and the floor plate, FGF-8 released by the midbrain-hindbrain organizer (MHO), FGF-4 released by the paraxial mesoderm and Wnt and TGF-beta have been shown to be key signaling molecules for the development and specification of serotonergic nuclei in the mammalian brain (Kiyasova and Gaspar 2011). Downstream transcriptional cascades play decisive roles in determining the functional and regional identity of serotonergic neurons. Expressed in temporal waves, transcription factors enable the step-wise cell fate choices and expression of functional genes of serotonergic neurons within the distinct rhombomeres. Early on, downstream of Shh signaling, the homeodomain transcription factor Nkx2.2 plays a decisive role in serotonergic specification, as Nkx2.2 knockout mice lack a majority of their serotonergic neurons and Nkx2.2 overexpression is sufficient for generating a majority of brain serotonergic neurons (Briscoe et al. 1999; Craven et al. 2004). In combination with Nkx2.2, Nkx6.1 also dictates serotonergic fate specification and Foxa2 promotes serotonergic specification by repressing a ventral motor neuron fate (Jacob et al. 2007; Vallstedt et al. 2001). Gata2 and Gata3 act downstream of Nkx transcription factors and only loss of Gata2 results in a complete loss of serotonergic neurons in the brain (Craven et al. 2004). Lmx1b and Pet-1 (FEV in humans) are among the next set of downstream transcription factors and are thought to be critical for the neurochemical identity of serotonergic neurons. They regulate the expression of proteins involved in serotonin processing and biosynthesis, including tryptophan hydroxylase 2 and the serotonin transporter. Lmx1b and Pet-1 continue to be expressed in serotonergic neurons throughout adulthood and are utilized as markers for labeling serotonergic neurons in vivo. Lmx1b mouse knockouts display a complete loss of serotonergic neurons, whereas Pet-1 mouse knockouts still have about 30% of raphe serotonergic neurons, highlighting the heterogeneity among serotonergic neurons (Kiyasova et al. 2011). Based on insights obtained from studies on raphe development in rodents, developmental signaling molecules and their downstream transcriptional programs have now been used to generate human serotonergic neurons in vitro.

For generating serotonergic neurons in vitro, in our protocol human fibroblasts were virally transduced with inducible overexpression constructs for ASCL1 and NGN2, two neurogenic transcription factors and NKX2.2, FEV, GATA2 and LMX1B, serotonergic fate factors (referred to as *S4F*). Pure populations of transduced fibroblasts were selected using geneticin and puromycin, and propagated before transdifferentiaton using neural conversion media containing a mix of small molecules and doxycycline. Small molecules are increasingly utilized for enhancing transdifferentiation efficiencies. Notably, inhibition of the TGFb/SMAD pathways with small molecules LDN-193189 or SB-431542, Wnt pathway activation with the GSK3b inhibitor CHIR99021 and increasing calcium signaling with cAMP and forskolin significantly increase neural transdifferentiation yields. For generating serotonergic neurons from fibroblasts, Xu et al. also virally transduced human fibroblasts with tetracycline-inducible transcription factors ASCL1, FOXA2, LMX1B, FEV and p53shRNA (referred to as *AFLVp*) but in the absence of pharmacological selection. For both the directed differentiation methods for generating serotonergic neurons, neural transdifferentiation efficiencies were about 60% with 20–40% serotonergic neurons. Acute hypoxia has been previously shown to boost neural transdifferentiation efficiencies and utilizing this strategy, Xu et al. (2016) showed that incubating cells in 5% O2 increased serotonergic differentiation to approximately 25%.

ASCL1 and NGN2 have been shown to be sufficient for direct conversion of fibroblasts to neurons and, in the context of serotonergic differentiation, Xu et al. (2016) showed that overexpressing FOXA2, LMX1B and FEV without ASCL1 reduced overall neuronal conversion. These data suggest that the primary role of ASCL1 is for promoting neural fate choice, rather than a serotonergic one. Together with our data, this suggests that transcription factors overlapping between our studies, ASCL1, FEV and LMX1B, may be the minimal set of core transcription factors sufficient for serotonergic differentiation in vitro. Interestingly, by testing different transcription factor combinations, Xu et al. (2016) showed that serotonergic differentiation efficiency decreased when NKX2.2, PITX3, NEUROD1, or miR124 were expressed in addition to AFLVp. These data suggest that these transcription factors may act to limit the pro-serotonergic effects of other serotonergic transcription factors, or may be redundant for a serotonergic cell fate choice.

Transdifferentiated serotonergic neurons obtained from each method express the rate-limiting enzyme required for serotonin biosynthesis, tryptophan hydroxylase (TPH). CNS-serotonergic neurons have been found to express TPH-2 and using a TPH-2 promoter-based fluorescent lentiviral reporter to sort out a relatively pure population of TPH-expressing neurons, we showed that iSNs were enriched for multiple human raphe-associated genes when compared to transdifferentiated glutamatergic neurons. While these data are promising, further studies are needed to understand the differences between in vitro and in vivo serotonergic neurons, given the entirely different environments and maturational states. Both iSNs and i5-HT neurons directly differentiated from fibroblasts displayed electrical activity. iSNs and i5-HT neurons exhibited induced and spontaneous action potentials. This correlates with the observation of higher serotonin in the culture medium in both studies and the observations by Xu

et al. that KCl-induced depolarization further increased extracellular serotonin levels (Xu et al. 2016). Strikingly, both studies showed that treatment of transdifferentiated serotonergic neurons with an SSRI resulted in increased serotonin concentrations, as did treatment with tryptophan in our study. The collective data from both studies demonstrate that fibroblast-derived serotonergic neurons are electrically active, can synthesize and release serotonin and maybe targeted by pharmacological manipulations (Table 1).

Several neural subtypes have been generated via reprogramming of fibroblasts, first to an intermediate pluripotent stem cell state followed by exposure to developmental cues. Here, iPSCs are differentiated using specific combinations of developmental signaling molecules as well as defined timelines. Using this strategy with hindbrain patterning cues, Lu et al. (2016) described a method for generating serotonergic neurons from human iPSCs. Their study showed that regulating the combination, concentration and sequence of exposure to key hindbrain signaling molecules, Shh, Wnt and FGF-4, is essential to serotonergic differentiation from iPSCs. Notably, Wnt pathway activation, achieved in a small window of Chir-99021 concentration (1.4 μM), promoted differentiation of serotonergic neurons with a rhombomere 2–3 identity. Lu et al. (2016) also showed that late-stage exposure to FGF-4 specifically enhanced expression of serotonergic transcription factors including FOXA2, while simultaneously repressing motor-neuron specification. These data suggest that precise levels and temporally regulated exposure to key developmental patterning cues is crucial for not only fate

specification but also regional identity (raphe and rhombomere). Their method generated 60% serotonergic neurons, expressing both TPH and serotonin. iPSC-derived serotonergic neurons display a characteristic low spontaneous oscillatory potential and long after hyperpolarization duration. Reassuringly, iPSC-derived serotonergic neurons released measurable amounts of serotonin, which increased following treatment with Escitalopram, a highly prescribed SSRI, or Tramadol, an SSRI and serotonin-releasing agent. It is interesting to note that all three methods generate serotonergic neurons that express the serotonin transporter, which is thought to be the primary target of SSRIs (Table 1).

Disease modeling with human serotonergic neurons

Each of the three methods efficiently generated human serotonergic neurons via different strategies and reassuringly, the derived serotonergic neurons expressed raphe-genes, generated serotonin, released serotonin and responded to SSRIs in vitro. iSNs, i5-HT neurons and iPSC-derived serotonergic neurons clearly share many defining properties but are likely to be different from each other in unique ways. While on the one hand direct differentiation technologies offer the advantage of speed for generating serotonergic neurons, iPSC-to-neuron differentiation captures the developmental sequence of patterning to produce serotonergic neurons with subtype identity. One can speculate that transdifferentiated serotonergic neurons could be made to adopt region-specific

Table 1 Key aspects of methods for generating human serotonergic neurons in vitro

|	Lu et al. 2016	Vadodaria et al. 2016a, b	Xu et al. 2016
Starting cells	iPSCs	Fibroblasts	Fibroblasts
Reprogramming required	Yes	No	No
	Key pathways activated	Transdifferentiation factors	Transdifferentiation factors
Serotonergic differentiation		Ascl1	
	Shh	Ngn2	Ascl1
	Wnt	Nkx2.2	Foxa2
	FGF-4	Fev	Fev
		Gata-2	Lmx1b
		Lmx1b	
Additional genetic targets	None	None	p53 shRNA
Special culture conditions	No	No	5% oxygen
Feeder cell layers utilized	None	Astrocytes	None
Electrophysiological activity	Evoked, spontaneous, low frequency	Evoked, spontaneous	Evoked, spontaneous
Marker expression assessment	QPCR, immunocytochemistry, western blot	Whole transcriptome, immunocytochemistry	QPCR, immunocytochemistry
Anatomical profile	Rostral raphe (R 2–3)	Unknown	Unknown
5-HT measurement method	HPLC	ELISA	HPLC
FDA-approved drugs tested	Escitalopram, Tramodol	Citalopram	Citalopram
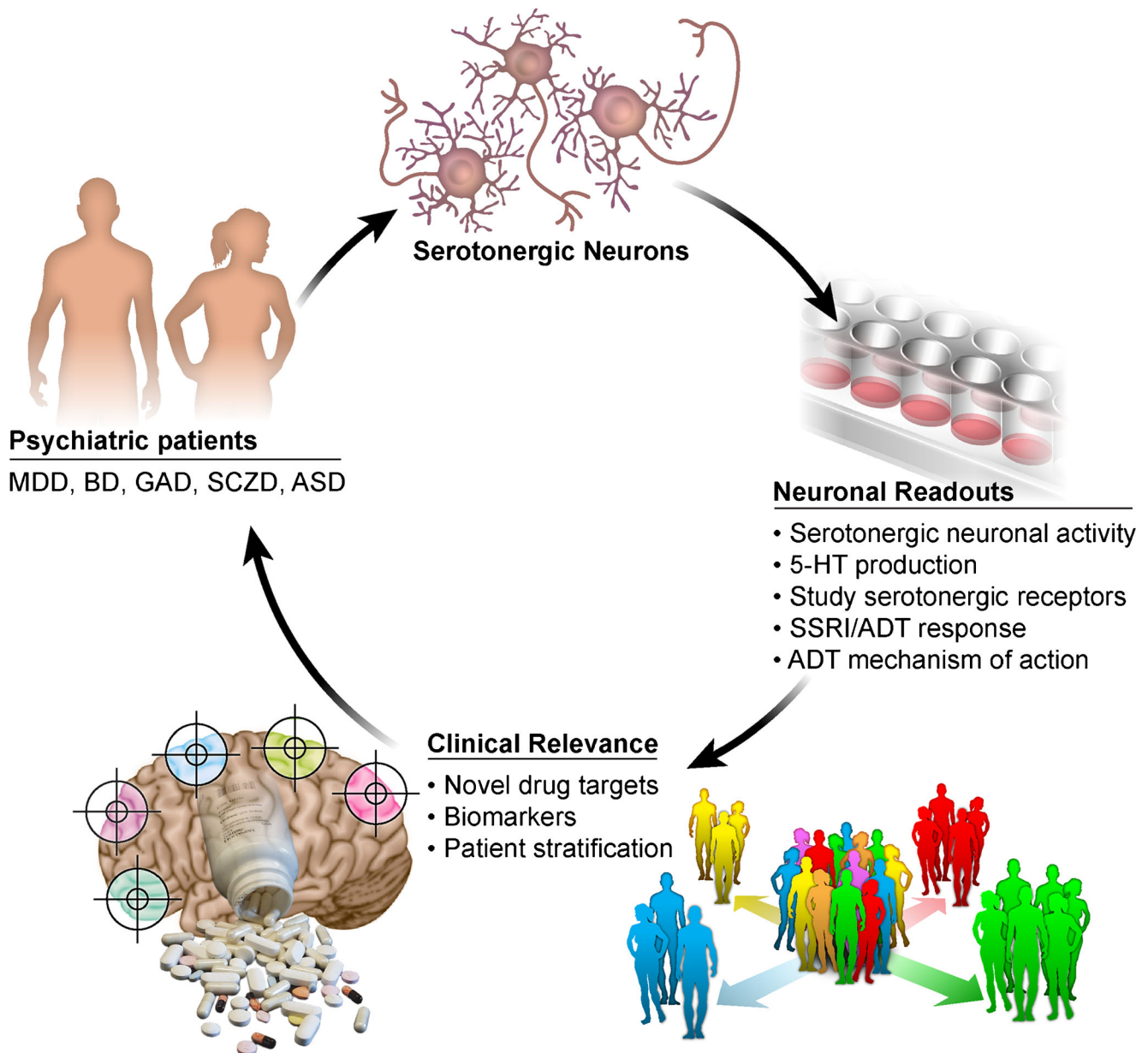
Figure 1. Serotonergic neurons for studying psychiatric disorders. Schematic shows how psychiatric-patient derived serotonergic neurons can be utilized for examining diverse in vitro phenotypes including differential activity, 5-HT (serotonin) production, serotonergic receptor activity, serotonin transporter activity, and antidepressant responses. In vitro serotonergic readouts could then contribute to the discovery of novel drug targets, biomarkers and may inform patient stratification in a clinically relevant mannerfor disorders such as Major depressive disorder (MDD), Bipolar disorder (BD), Generalized anxiety disorder (GAD), Schizophrenia (SCZD), Autism spectrum disorder (ASD).

serotonergic identities. Given that Shh, Wnt and FGF-4 promote regionalization via downstream transcription factors, there exists the possibility that overexpression of fate-determining transcription factors, exposure to signaling molecules, or an optimal combination of both could give rise to directly differentiated serotonergic neurons with in vivo-like regional identity. For a better understanding of the optimal use of each 'kind' of serotonergic neuron for disease modeling using patient fibroblasts, further studies are required to firstly compare them to each other and, secondly, to compare them to

serotonergic neurons in the brain. For example, it would be interesting to study how the derived serotonergic neurons mature in vitro or following transplantation in vivo. One could ask whether the developing serotonergic neurons display the full repertoire of in vivo features, including the expression of multiple receptors, neuropeptides and co-neurotransmitters. The choice of method for generating patient-derived serotonergic neurons will depend on the specific questions as well as the nature of the patient cohort. For example, the transdifferentiation process itself may complicate the study

of some serotonergic phenotypes, where overexpressed serotonergic transcription factors may mask potential phenotypes. On the other hand, iPSC-derived serotonergic neurons may not be mature enough for studying adult raphe-related phenotypes. Future methodological studies would also need to address whether modifications of existing protocols could capture the diversity of in vivo serotonergic neurons. To understand how in vitro serotonergic neurons compare human serotonergic neurons, one could compare transcriptomic data from each, utilizing available expression databases (e.g., Allen Brain Atlas). Further studies that compare in vitro-derived serotonergic neurons to their in vivo counterparts would help determine how they may be best utilized for disease modeling. Currently, much of our knowledge on cellular aspects of serotonergic neurotransmission in vivo comes from rodent studies and studying human serotonergic neurons in vitro may give us insights into species-specific differences. Given the unique and overlapping features of in vitro-derived serotonergic neurons, each could serve as a complementary approach for studying certain aspects of serotonergic neurotransmission in the context of psychiatric disorders.

It is becoming increasingly clear that gaining novel insights into the biology of psychiatric disorders requires a multipronged approach, consisting of but not limited to, cell-based diseased modeling. Since their development over 10 years ago, reprogramming and transdifferentiation technologies have raised new hope for disease modeling and in vitro drug screening using patient-derived cells (Parr et al. 2017). Mood disorders have overlapping symptoms and therapies, probably due to their complex and overlapping genetic, epigenetic and environmental contributors. Unlike neurological disorders with neurodegenerative components, neuropsychiatric disorders do not appear to be the result of a loss of any particular cell type and deficits in serotonergic neurotransmission appear to be nuanced. Hence, cell replacement would not be the aim of generating patient-derived neurons but studying components of serotonergic neurotransmission using patient-derived neurons may offer new insight into the cellular mechanisms underlying some psychiatric disorders. In the current state, generating serotonergic neurons from psychiatric patients would take at least 6 weeks, not offering value for the purposes of immediate diagnosis but in the long run would contribute to patient-stratification based on genetic and cellular differences (Fig. 1). Patient-derived serotonergic neurons could also be used to examine whether patients would differentially respond to therapeutic drugs that directly target components of the serotonin system. Study designs that incorporate known genetic variants and well-characterized patient cohorts would enable the testing of key hypotheses in the field and promote the development of assay platforms for ascertaining the role of altered serotonergic neurotransmission in neuropsychiatric disorders. Thus, in vitro-generated human serotonergic neurons represent a first step in exploring the utility of patient-derived serotonergic neurons for studying psychiatric disorders in the future.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

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