Review

Serotonin research: contributions to understanding psychoses

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The history of serotonin research is closely related to the study of hallucinogenic drugs that function as agonists at serotonin-2A receptors. The fundamental idea that psychotic states seen in psychiatric disorders such as schizophrenia might be attributable, in part, to abnormalities in serotonergic systems began with the almost simultaneous discovery of lysergic acid diethylamide (LSD), psilocybin and serotonin. Sixty years of study have confirmed early speculations regarding the important relationship between serotonin and both drug-induced and disorder-based psychotic states. Now, modern biochemical, pharmacological, behavioral, neuroimaging, genetic and molecular biological sciences are converging to understand how serotonergic systems interact with other monoaminergic and glutamatergic systems to modulate states of consciousness and contribute to psychotic disorders such as the group of schizophrenias. This review summarizes experimental assessments of the serotonergic hallucinogen model psychosis in relation to the serotonin hypothesis of schizophrenia.

Introduction

The history of research on serotonin, or 5-hydroxytryptamine (5-HT), is closely intertwined with modern studies of the neurobiological origins of psychotic states in general and the group of schizophrenia disorders in particular. Among the defining events that led to this early association were the discoveries of the psychosis-like effects of lysergic acid diethylamide (LSD) by the late Albert Hofmann (Sandoz, www.sandoz.com) and the identification, less than a decade later, of serotonin as an endogenous neurohormone. As summarized in Table 1, the concept that the drug-induced psychotic state induced by LSD is attributable to either antagonist or agonist actions at serotonin receptors rapidly led to the suggestion that LSD provides a model psychosis. This concept prompted the fundamental hypotheses that abnormalities of serotonin function are responsible for psychiatric disorders such as the spectrum of schizophrenia disorders and, therefore, that serotonin agonists or antagonists might be useful in the treatment of schizophrenia. Experimental studies have confirmed early descriptions [1] of striking similarities between psychotic states in psychiatric disorders and the subjective reports of subjects under the influence of psychedelic drugs. Serotonergic hallucinogens such as LSD or the naturally occurring compound psilocybin produce profound changes in mood, thought, intuition, sensory perception, the experience of time and space, and even the experience of self. In these states, perceptual hypersensitivity, illusions and elementary hallucinations are common. In general, the intensity of these alterations of perception and consciousness are dose dependent, so that hallucinations involving disorientation in person, place and time rarely, if ever, occur with low-to-medium doses [2,3]. Depending upon the individual, the individual's expectations and the setting, the same hallucinogen might produce a loss of ego boundaries combined with elevated mood states ranging from pleasure to bliss and feelings of oneness, or might lead to more psychotic ego dissolution including fear and paranoid ideation associated with experiences of split ego [4]. Such experiential phenomena are otherwise rarely reported except in dreams, contemplative or religious exaltation, and acute psychoses [5–7]. Thus, the discovery of the effects of LSD led rapidly to the suggestion that serotonergic hallucinogens provide model psychoses and, more generally, to the serotonin hypothesis of schizophrenia. The subsequent experimental assessment of these hypotheses and the new directions of research engendered by this line of work are discussed here.

Parallels between dose-related hallucinogen effects and the development of schizophrenia

Systematic comparisons of the symptom profiles associated with serotonergic hallucinogens and schizophrenia disorders have demonstrated robust qualitative similarities with the earliest phases of schizophrenic psychoses, with fewer similarities being evident in the chronic phases of the illnesses [8–12]. The heightened awareness and euphoria reported by some healthy volunteers treated with psilocybin or the phenalkylamine hallucinogen mescaline in addition to the negative affective experiences of other individuals, especially at higher doses, are consistent with evidence that the earliest affective changes in schizophrenic patients range from pleasurable or exhilarating to anxious and depressed [13,14]. Thus, several authors have argued that hallucinogen-induced states share some common phenomenological features with early acute stages of the group of schizophrenia disorders [12]. Certainly, no transient state produced by the acute administration of a drug could possibly mimic the entire syndrome and course of the complex group of disorders subsumed under the term schizophrenia. Despite the number of

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Table 1. Milestones in serotonin and hallucinogen research

Date	Author(s)	Refs	Discovery
1943	Hofmann	[6]	LSD produces psychotomimetic effects
1947	Stoll	[1]	LSD effects are similar to schizophrenia
1948	Rapport	[58]	Serotonin identified as a neurohormone
1954	Gaddum and Hammeed	[59]	LSD suggested to be a serotonin antagonist
1954	Woolley and Shaw	[39]	Serotonin suggested to be involved in etiology and treatment of psychotic disorders
1956	Shaw and Wooley	[40]	LSD suggested to be a serotonin agonist; serotonin antagonists suggested to treat schizophrenia
1958	Hofmann	[60]	Psilocybin structure and synthesis reported; provides research tool for model psychosis studies

similarities between hallucinogen-induced models and psychoses in schizophrenia, some differences are also apparent. One striking difference is that the essentially lifelong nature of schizophrenia disorders contrasts with the rapidity with which tolerance develops to the psychological effects of serotonergic hallucinogens. Whether tolerance occurs to all serotonergic hallucinogens, however, remains debatable [15]. Another difference is that auditory rather than visual hallucinations are more characteristic of schizophrenia, whereas visual disturbances are more common with hallucinogens. However, evidence that visual hallucinations occur more often in acute and incipient stages than in chronic schizophrenic patients [16,17] is another indication that the drug-induced states are most relevant to phenomena occurring at the onset of schizophrenia disorders.

The changes in the qualitative features of schizophrenia disorders across the progressive course of the illness might have some parallels with the alterations in the predominant experiences produced by hallucinogenic drugs as the dosages are increased (Box 1). In both cases, there is a continuum or progression from non-threatening alterations of consciousness dominated by heightened sensations and perceptions through dramatic and overwhelming

Box 1. Symptoms in psychotic disorders and hallucinogen states

Psychosis is a generic psychiatric term for a mental state characterized by a 'loss of contact with reality'.

Signs and symptoms of psychosis

- Perceptual disturbances (e.g. illusions and hallucinations)
- Delusions (firmly held erroneous beliefs due to distortions or exaggerations of reasoning and/or misinterpretations of perceptions or experiences)
- Thought disorder (formal, thought blocking or flight of ideas)
- Disorder of emotion (inappropriately low or high)
- Lack of insight into the unusual, strange and bizarre nature of one's experience and behavior

Classification of psychotic illnesses

Some patients will have only one short episode of psychosis, others will progress into a psychotic illness such as the schizophrenia spectrum disorder, schizoaffective disorder and affective psychosis including mania, psychotic depression and mixed affective psychosis.

Development and course of psychotic illnesses

Prodromal phase

- Visual perceptual disturbances (e.g. blurred vision, partial seeing and hypersensitivity to light)
- Acoustic perceptual disturbances (e.g. hypersensitivity to sound or noise, or acoasms)
- Ideas of reference
- Odd beliefs or magical thinking
- Thought interferences, pressure or blockages
- Unstable ideas of reference
- Derealization
- Decreased ability to discriminate between ideas and perception, fantasy and true memories
- Suspiciousness or paranoid thinking
- Intermittent psychotic symptoms: hallucinations, delusions, formal thought disorder, gross disorganized or catatonic behavior

First psychotic episode

Positive symptoms of schizophrenia:

- Disorders of perception: hallucinations: auditory, visual, olfactory, tactile, visceral, bodily distortions or hallucinations
- Delusions: delusions of grandeur, delusion of persecution or nihilistic delusions
- Disorder of thought: disorder of form or possession of thought
- Disorder of insight
- Grossly disorganized or catatonic behavior

Negative symptoms of schizophrenia:

- Disorder of emotion; for example, alteration in nature (low or high), in reactivity or inappropriate reactions
- Affective flattening
- Poverty of speech
- Avolition

Chronic schizophrenia:

- Recurrence of positive and negative symptoms

Basic dimensions of hallucinogen-induced altered states [4]

Oceanic boundlessness

- Positively experienced loosening or loss of ego-boundaries, feelings of oneness, religious exaltation
- Derealization, altered sense of time
- Positive, heightened or mania-like mood
- Magical thinking

Visionary restructuralization

- Visual illusions and hallucinations
- Synaesthesias
- Changed meaning of percepts
- Decreased ability to discriminate between ideas and perception, fantasy and true memories

Anxious ego-disintegration

- Depersonalization, split of ego
- Thought disorder
- Delusional or paranoid thinking
- Anxiety, panic
- Motor abnormalities

Acoustic alterations

- Hypersensitivity to sound or noise, acoasms
- Hallucinations (voices)

Altered vigilance

changes in perception and moving to a fragmentation of consciousness and eventually to a disturbing ego-dissolution. For example, the hallucinatory disintegration and the loss of self-control over thought processes and intentionality observed in psilocybin-induced psychoses are highly reminiscent of acute schizophrenic decompensation. In addition, progressive increases in negative symptoms, such as emotional and social withdrawal, could reflect efforts to protect the individual from input overload characteristic of the initial disturbance. One might speculate that the early phases of schizophrenia disorders are dominated by neurobiological abnormalities involving abnormalities in serotonin receptors (presumably 5-HT_{2A}, see later), but that the subsequent course of the disease involves a more complex evolution of compensatory alterations involving serotonergic systems and interacting dopaminergic and glutamatergic systems.

Experimental studies of the model psychosis induced by serotonin agonists

A commonality among many theoretical descriptions of the neuronal basis of the symptomatology in schizophrenia and other psychotic disorders is the basic idea that deficits in early information processing engender the cognitive disturbances and even the psychotic symptoms observed in psychotic disorders in psychiatry [18–20]. The notion is that an underlying dysfunction of information-processing mechanisms in the schizophrenia spectrum involves an inability of these patients to screen out, inhibit, filter or gate extraneous stimuli and to attend selectively to salient features of the environment. Such failures of attentional gating mechanisms might overload patients with excessive processing of both sensory and cognitive stimuli, which, in turn, could lead to a breakdown of cognitive integrity and difficulty in distinguishing self from non-self [21,22]. Such descriptions in the literature on schizophrenia are clearly mirrored in many descriptions of hallucinogenic drug action, as detailed elsewhere [7,15,22].

The theoretical construct of gating has been operationalized successfully by using measures of behavioral plasticity such as prepulse inhibition and habituation of acoustic startle responses, auditory gating, binocular rivalry and a host of neurocognitive paradigms (Box 2). Symptomatic schizophrenia patients, including never-medicated first-episode patients in the acute phase of the illness [23], exhibit deficits in both prepulse inhibition and habituation of startle, phenomena that are correlated with measures of thought disorder [24]. Although most thoroughly studied in schizophrenia-spectrum patients, such abnormalities – like almost all symptoms and signs of psychoses – are not specific to schizophrenia, but are observed in what is often considered to be a family of gating disorders [18]. Mimicking these psychiatric gating disorders, serotonergic hallucinogens reduce prepulse inhibition and habituation in rodents [25] and prepulse inhibition in humans [26]. As with these measures of pre-attentive sensorimotor gating, psychopharmacological studies of the serotonergic psychedelic psilocybin demonstrate dose-dependent behavioral impairments in healthy subjects that mimic those seen in schizophrenia, including deficits in attention, working memory and associative learning, while leaving executive functions largely unaffected [27,28]. Serotonergic hallucinogens also impair high-level but not low-level motion perception and reduce binocular rivalry rate and rhythmicity in a manner reflecting subjective changes in conscious state [27]. Current available data indicate that serotonergic hallucinogens disrupt information processing in cortico–striato–pallido–thalamic pathways that have been implicated in sensory gating of internal and external information to the cortex and notably also in the pathophysiology of schizophrenia [22]. Because, as discussed later, these hallucinogenic effects seem to be related primarily to agonist actions at serotonin receptors, the long-standing serotonin hypothesis of at least the incipient stages of schizophrenia remains viable today.

The hypothesis that 5-HT_{2A}-receptor agonists such as LSD and psilocybin have effects that mimic schizophrenia-like psychotic states has received renewed support in recent years. First, it has now been demonstrated experimentally in humans that the indoleamine hallucinogen psilocybin produces psychotomimetic effects through excessive 5-HT_{2A}-receptor activation [27,28], confirming the evidence for this mechanism from extensive animal studies. Second, 5-HT_2-receptor abnormalities are evident in the brains of schizophrenic patients [22]. Indeed, 5-HT_{2A}-receptor densities are reduced in the prefrontal cortex in drug-naive schizophrenic patients and in at-risk subjects, indicating that early abnormalities of serotonergic neurotransmission might predate the onset of schizophrenia [29,30]. Such findings have prompted the suggestion that psychopharmacological manipulations be considered to address the apparent vulnerability to schizophrenia associated with abnormalities in 5-HT_{2A} receptors

Box 2. Measures of behavioral plasticity and gating

Habituation of startle
Habituation is the progressive decrement of responding to the repeated presentations of a stimulus – in this case, a startling acoustic stimulus – in the absence of any environmental consequences predicted by the stimulus. Startle is measured in humans as the magnitude of the eyeblink reflex and in animals as a whole-body flinch response. Habituation is considered to be the simplest form of non-associative learning and is a prerequisite to selective attention to relevant stimuli.

Prepulse inhibition of startle
Prepulse inhibition refers to the unlearned reduction in the startle response when the startling stimulus is preceded 30–500 ms earlier by a weak non-startling prepulse in the same or different sensory modality. It is considered to reflect pre-attentive sensorimotor gating functions.

Auditory gating
Auditory gating in this context refers to the reduction in the second of two event-related potentials, measured via electrodes on the scalp, when two weak auditory clicks are presented at an interval of 500 ms. It is considered to be a form of sensory gating and to reflect short-term habituation.

Binocular rivalry
Binocular rivalry occurs when two different and conflicting images are presented simultaneously to each eye and the observer experiences repeated switches between the visual awareness of the two images.

[29]. Third, the role of 5-HT_{2A}-receptor antagonism is known to contribute to the effects of atypical antipsychotics such as clozapine and risperidone in patients and in animal models of schizophrenia [31,32]. Fourth, positron emission tomography (PET) studies conducted in healthy humans reveal that psilocybin produces metabolic changes indicative of hyperfrontality, which parallels the hyperfrontality characteristic of the acute phase of schizophrenia [14,33] and contrasts with the hypofrontality seen in chronic patients with deficit schizophrenia [34]. Interestingly, in one study, prefrontal hyperperfusion correlated with formal thought disorder and grandiosity in drug-naive schizophrenic patients, whereas negative symptoms persisting after neuroleptic treatment correlated with cortical and thalamic hypoperfusion [35]. Prefrontal-cortex and anterior-cingulate activity also correlated with positive symptoms in drug-free schizophrenia patients [34]. A similar association between activation of prefrontal and cingulate cortex and transient exacerbation of positive psychotic symptoms was reported in chronic schizophrenic patients during ketamine challenge [36]. Taken together, these findings indicate that metabolic hyperfrontality and presumably also increased thalamic activity [33], rather than hypofrontality as seen in chronic schizophrenia, are pathophysiological manifestations of certain acute psychotic symptoms induced by either drugs or psychiatric disorders. Furthermore, recent investigations have provided genetic evidence linking schizophrenia and 5-HT_{2A} receptors via measures of the sensorimotor gating deficits seen in human and animal studies of serotonergic hallucinogens, and schizophrenia patients and models. Specifically, both the A1438G and T102C polymorphisms in the gene encoding the 5-HT_{2A} receptor are significantly associated with deficits in both prepulse inhibition and habituation of startle in patients with schizophrenia [37]. As reviewed in Ref. [37], the T102C-C variant of the T102C polymorphism carried by patients exhibiting poor sensorimotor gating has been associated previously with schizophrenia, poor long-term outcome and poor response to antipsychotic treatments, and, recently, with an array of cognitive functions [38].

Serotonin receptors involved in psychotomimetic effects

The initial uncertainty in the mid-1950s (Table 1) as to whether serotonergic hallucinogens such as LSD or psilocybin function primarily as serotonin agonists or antagonists [39,40] continued well through the 1980s. As reviewed in Ref. [15], studies using different model systems indicated that LSD is an agonist, a partial agonist or even an antagonist at serotonin receptors. Suffice it to say that the accumulated evidence from biochemical, electrophysiological and behavioral studies in animals clearly demonstrate that both indoleamine and phenylethylamine hallucinogens produce their psychological effects primarily by agonist actions on serotonin receptors in the brain [15,41,42]. Furthermore, the preponderance of evidence indicates that 5-HT_{2A} receptors, in particular, contribute most substantially to the effects of hallucinogens. In rodent behavioral paradigms ranging from exploratory behavior, habituation or prepulse inhibition of startle, simple forms of classical or instrumental learning and assessments of drug-discrimination properties, the 5-HT_{2A} subtype of serotonin receptors was found to be principally responsible for the effects of classical hallucinogens [15,25,43]. More importantly, recent clinical studies in humans have confirmed this conclusion, demonstrating, for example, that the selective 5-HT_{2A}-receptor antagonist ketanserin blocks the key psychological effects of the hallucinogen psilocybin in human volunteers [27,28]. These results provided the most compelling and conclusive proof of 5-HT_{2A}-receptor mediation of the effects of hallucinogens in humans.

Despite evidence that antagonist actions at 5-HT_{2A} receptors contribute to the added clinical benefits of the newer generation of antipsychotic drugs (i.e. 'atypicals') [32] that are used to treat psychotic symptoms in patients with schizophrenia, bipolar disorder and depression, there is, as yet, little support for the possible antipsychotic effects of selective antagonists at 5-HT_{2A} receptors. Animal-model studies indicate that selective 5-HT_{2A}-receptor antagonists, most of which seem to be inverse agonists at 5-HT_{2A} receptors [44], would be effective in the treatment of patients with schizophrenia who are not responsive to typical antipsychotics that function primarily via dopamine-receptor antagonism [43,45]. Such clinical studies, however, have not been reported. In a Phase III clinical trial of treatment-responsive patients with schizophrenia, the 5-HT_{2A}-receptor inverse agonist M100907 was efficacious relative to a placebo but less efficacious than haloperidol. A small Phase II study indicated similar antipsychotic efficacy for another 5-HT_{2A}-receptor antagonist, eplivanserin [46]. Interestingly, a newer 5-HT_{2A}-receptor inverse agonist, pimavanserin, is being examined for efficacy in the treatment of psychotic symptoms in patients with Parkinson's disease, for whom typical antipsychotics are contra-indicated (http://clinicaltrials.gov/ct2/show/NCT00477672).

Although 5-HT_{2A} receptors seem to be the most important, the activation of 5-HT_{1A} receptors might also influence many of the same behavioral endpoints and might contribute to and/or interact with the impact of hallucinogens on 5-HT_{2A} receptors [15,41]. Moreover, because LSD, *N*,*N*-dimethyltryptamine (DMT), 5-methoxy-DMT and psilocybin display high affinity for and function as agonists at 5-HT_{1A} receptors, the possible contributions of 5-HT_{1A} receptors to the generation of psychosis in humans remains uncertain [24]. 5-HT_{2C}-agonist actions are unlikely to contribute to the symptomatology of schizophrenia because MK-212 is an agonist at 5-HT_{2C} receptors and is not psychotomimetic, and another 5-HT_{2C}-receptor agonist is being evaluated currently in clinical trials as a possible antipsychotic (http://clinicaltrials.gov/ct2/show/NCT00265551) [46,47]. Possible contributions of the 5-HT_4, 5-HT_5, 5-HT_6 or 5-HT_7 receptors also await further study.

Serotonin circuits and interactions with other systems

Early research into the effects of serotonergic hallucinogens and hallucinogenic anesthetics (e.g. phencyclidine and ketamine) on brain electrical activity in animals indicated that the key psychological effects of these drugs arise along a continuum of excitation. Specifically, after an

initial excitation characterized by electro-encephalographic (EEG) desynchronization and psychomotor activation, all of these drugs induce a state with intermittent bursts of hypersynchronous 2.5-Hz EEG wave patterns associated with hallucinatory behavior and then a state with continuous hypersynchrony associated with more intense bizarre postures and hallucinatory movements [48]. The observation that sensory-evoked responses are increased during the initial phase of desynchronization and further enhanced during the subsequent phases of hypersynchrony led to the suggestion that the characteristic evolution from sensory illusions to pseudo and true hallucinations in humans arises with the increasing impairment and disruption of sensory gating and a subsequent overload of higher-order areas of sensory-information processing [48,49].

Functional neuroimaging studies in humans demonstrate that psilocybin produces marked activations of regions in the prefrontal cortex, anterior cingulate and insula, whereas smaller activations were found in the parietal cortices and thalamus. By contrast, deactivations were found in striatal regions, the occipital cortex and the visual pathway [14,22] (Figure 1). This hyperfrontality and divergent prefrontal–subcortical activation was corroborated in further studies with both psilocybin and the classic phenylethylamine hallucinogen mescaline [13,50]. Moreover, a comparison of serotonergic hallucinogens with hallucinogenic doses of glutamatergic *N*-methyl-D-aspartate (NMDA) antagonists in humans revealed that ketamine also produces a metabolic hyperfrontality and comparable changes in regional brain activity in cortical and subcortical structures [14,22,34]. Taken together, these findings indicate that the common hyperfrontality and cortical activation pattern induced by serotonergic and glutamatergic hallucinogens is due to a common disruption of thalamic gating of sensory and cognitive information [21,22]. Specifically, it is proposed that the thalamus within cortico–striato–thalamo–cortical (CSTC) feedback loops is crucial in gating or filtering out external and internal information to the cortex and, thereby, in the regulation of the level of awareness and attention. Evidence from animal studies indicates that thalamic gating is under the control of glutamatergic cortico–striatal pathways projecting to the dorsomedial (MD) and reticular nuclei of the thalamus in addition to being under the modulatory influence of serotonergic and dopaminergic projections arising from the raphe and ventral tegmentum to several components of the CSTC loops [22,51] (Figure 2).

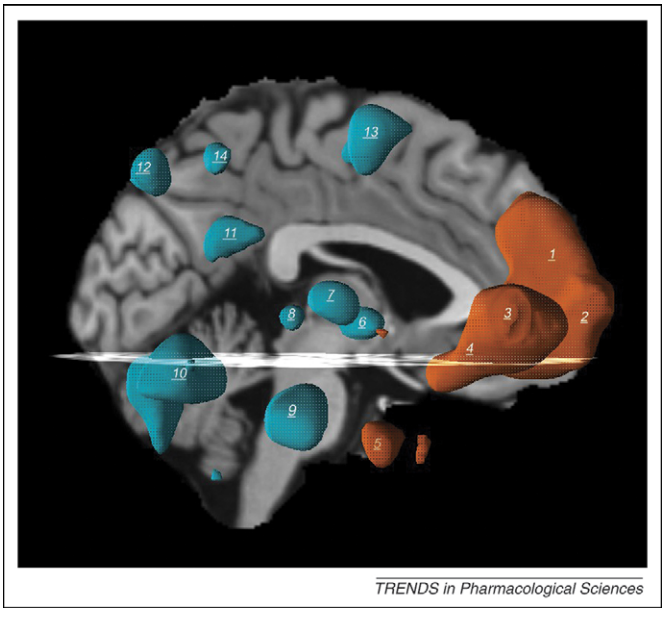

Figure 1. Effects of psilocybin on brain activity. The effects of psilocybin (0.26 mg kg^{-1} taken orally) on regional brain activity during a simple visual-guided motor-response task in healthy human volunteers are displayed as indexed by changes in cerebral blood flow (CBF) using H_2O-PET ($n = 11$). Red shows relative increases and blue indicates relative decreases in regional brain activity. Psilocybin produced a marked prefrontal activation (hyperfrontality) in areas that are important in cognitive and affective processes such as the anterior cingulate (1), frontomedial (2) and dorsolateral (3) cortices, insula (4) and temporal poles (5). Decreased activation was observed in brain areas important for gating or integrating cortical information processing such as bilateral thalamus (7,8), right globus pallidus (6), bilateral pons (9) and cerebellum (10). Psilocybin also reduced neuronal activity in somatosensory areas (14) and components responsible for higher-order visuo-spatial processing such as precuneus (12) and angular gyrus (11), in addition to supplementary eye fields of the pre-motor area (13) (F.X. Vollenweider, unpublished).

As shown in Figure 2, serotonergic hallucinogens can alter thalamocortical transmission by stimulation of 5-HT_{2A} receptors located in several components of the CSTC loop, including the prefrontal cortex, striatum, nucleus accumbens and thalamus. This cortical inundation with sensory and cognitive information, in turn, could ultimately cause the sensory flooding, cognitive fragmentation and ego-dissolution seen in both drug-induced and disorder-based psychoses [14,33]. This view is supported by the fact that infusion of a 5-HT_{2A} agonist in to the ventral pallidum, a component of the CSTC loop, in rodents [52] and systemic administration of psilocybin in humans disrupts sensorimotor gating as indexed by prepulse inhibition of startle [26]. Furthermore, a correlational analysis revealed that the changes in the perception of time and space and the pleasurable loosening of ego-boundaries are correlated positively with the activation of a frontolimbic–parieto–occipital network and correlated negatively with ventral striatal, hippocampal and left-amygdalar activity [14]. By contrast, the severity of anxious ego-dissolution related to loss of control, thought disorder and the experience of a fragmented self correlated positively with metabolic activity in the thalamus and left temporomedial cortex and negatively with activity in the orbitofrontal cortex and adjacent anterior cingulate. Thus, it seems that anxious ego-dissolution and associated thought disorder depend mainly on thalamic overactivity and orbitofrontal underactivity. Thalamic and left-medial-temporal-lobe overactivity was also associated with reality distortion [33] in schizophrenia. Although this finding could be a sign of enhanced thalamic transmission and support the view that deficient thalamic gating leads to sensory overload of the cortex and psychosis, it could also indicate that serotonergic hallucinogens also lead to a disruption of cortico–thalamo–cortical or cortico–cortical integration of distributed neuronal activity ('binding'). Specifically, it has been suggested that the key neural mechanism underlying a coherent conscious experience involves the re-entrant interactions between posterior thalamo–cortical areas subserving perceptual categorization and anterior areas related to concept formation, value-related memory and planning [53]. Whether the dissociated experience of the

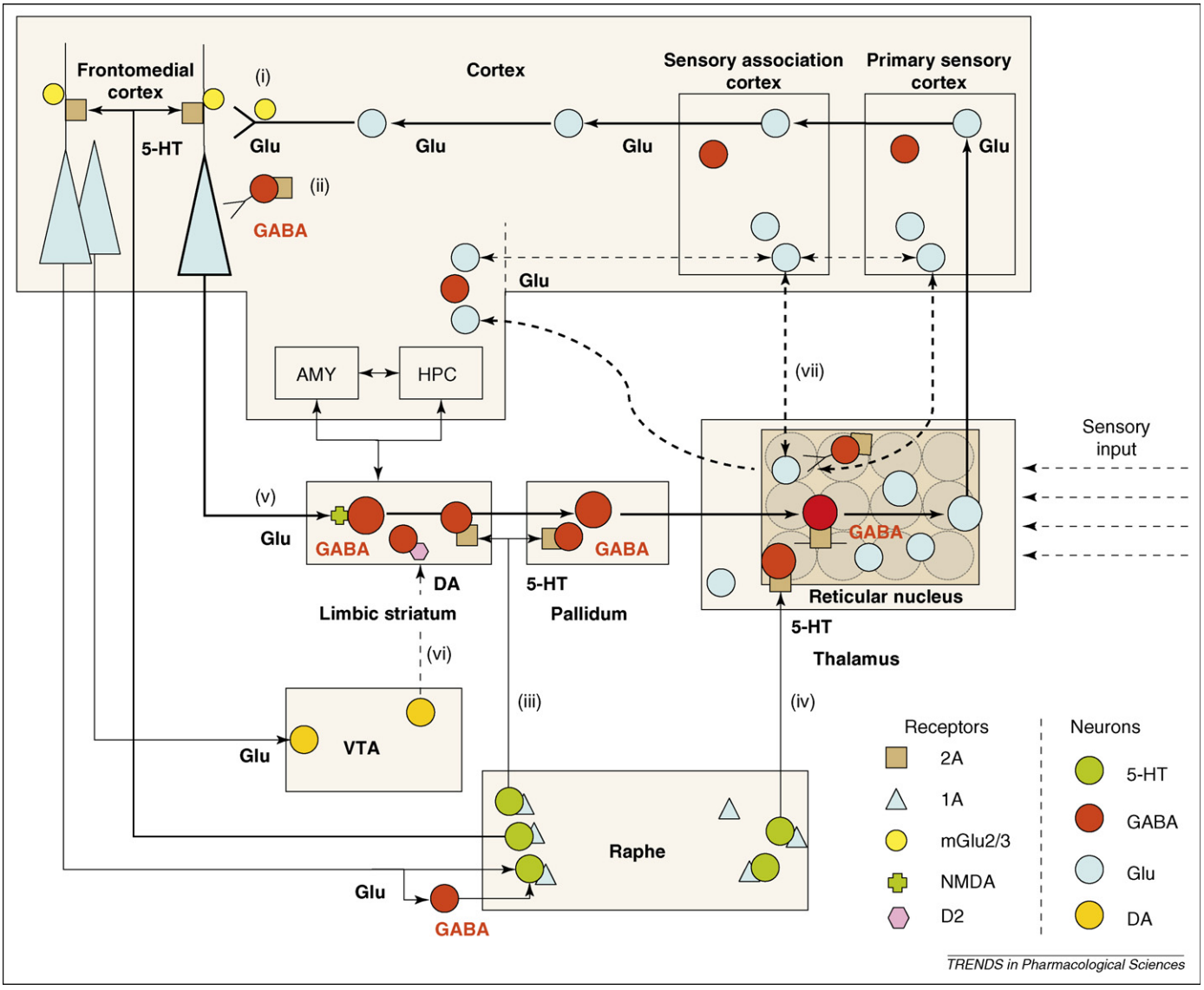

Figure 2. The thalamic filter and integrator model. The thalamus, within limbic cortico–striato–(pallido)–thalamo–cortical (CSTC) feedback loops, is proposed to function as a filter in the gating of extero- and interoceptive sensory and cognitive information to the cortex and, within cortico–thalamo–cortical (CTC) re-entrant pathways, it is proposed to be crucial in integrating cortically categorized exteroceptive perception with internal stimuli of the memory and value system. Thalamic gating is under the control of glutamatergic cortico–striatal pathways projecting to the dorsomedial (MD) and reticular nuclei of the thalamus and under the modulatory influence of serotonergic and dopaminergic projections arising from the raphe and ventral tegmentum (VTA) to several components of the CSTC loops (for details, see Ref. [22]). The model predicts that serotonergic hallucinogens disrupt thalamic gating and produce sensory overload of the prefrontal cortex by excessive stimulation of 5-HT_{2A} receptors located in several components of the CSTC loop, including the prefrontal cortex (i and ii), limbic striatum (iii) and thalamus (iv). The blockade of NMDA-mediated glutamatergic (Glu) cortico–striatal neurotransmission (v) (e.g. by ketamine) or the increase of mesolimbic dopaminergic (DA) neurotransmission (vi) (e.g. by D-amphetamine) could lead to a similar neurotransmitter imbalance in CSTC loops, which again results in an opening of the thalamic filter, sensory overload of the cortex and psychosis. In addition, the excessive stimulation of thalamic and/or cortical 5-HT_{2A} receptors located on GABAergic interneurons by hallucinogens could lead to a disruption of CTC or cortico–cortical integration of distributed neuronal activity ('binding') (vii), which, in turn, might underlie the more anxious and fragmented experience of ego-dissolution that is often reported after high doses of hallucinogens. Although application of serotonergic hallucinogens into the frontal cortex in rodents has been demonstrated to increase pyramidal-cell activity via stimulation of 5-HT_{2A} receptors located on apical dendrites of pyramidal cells (i) and/or GABAergic neurons (ii), it remains unclear whether such a local activation without a subsequent disruption of thalamic gating or integration of information processing leads to psychosis in humans or simply to excitation and/or increased sensory awareness. Abbreviations: VTA, ventral tegmental area; AMY, amygdala; HPC, hippocampus; 5-HT, serotonin, DA, dopamine, Glu, glutamate; receptors: 2A, 5-HT_{2A}; 1A, 5-HT_{1A}; mGlu2/3, metabotropic glutamate receptor subtypes 2 and 3; NMDA, *N*-methyl-D-aspartate; D2, dopamine D_2.

self in hallucinogenic states is due to disrupted dynamics of cortico–thalamic and cortico–cortical re-entrant interactions, as has been reported recently in schizophrenia patients, needs to be further investigated [53].

New directions for research on serotonin and psychosis

Despite the extensive research linking serotonin and psychosis over the past six decades, exciting new findings are now prompting studies of novel mechanisms that could further our understanding of the neurobiology of drug- and disease-induced psychoses. Experimental approaches ranging from molecular biology to behavioral studies indicate that the unifying principle of 5-HT_{2A}-agonist actions as mediating the psychedelic and psychotomimetic effects of serotonergic hallucinogens is over-simplified. Sophisticated measures of behavioral phenomena in both animals and humans have revealed new insights relevant to some effects of serotonergic hallucinogens. It is now clear that some behavioral effects of drugs such as psilocybin (even effects that were conceptualized as being relevant to altered states of consciousness and potentially psychotic states) seem to be independent of the classical 5-HT_{2A}-

receptor-agonist actions. Because the switch rate in a binocular rivalry paradigm provides a measure of perceptual grouping and attention that is altered in psychotic states, it has been examined in the model psychosis paradigm elicited by administration of psilocybin to healthy volunteers. Although psilocybin reduced switch rates as predicted, this effect was not diminished by pretreatment with the 5-HT_{2A} antagonist ketanserin at a dose that was effective in preventing the positive psychosis-like symptoms induced by psilocybin in the same subjects [27]. Thus, this presumably psychosis-related perceptual phenomenon is affected by the serotonergic agonist psilocybin, but apparently not via classical 5-HT_{2A}-agonist actions. Future studies will need to examine whether non-5-HT_{2A} serotonin receptors, such as 5-HT_{1A} or others for which psilocybin has moderate affinity, are responsible for these ketanserin-insensitive behavioral effects. If so, the possible relevance of these other receptors in either the etiology or treatment of specific aspects of schizophrenia disorders should be considered.

Intriguing new evidence indicates that important differential pharmacological functions might be evident even within the domain of 5-HT_{2A}-receptor-agonist actions. Among the long-standing mysteries related to the putative relationship between 5-HT_{2A}-receptor agonism and psychotomimetic profiles is the fact that lisuride, a congener of LSD, is not hallucinogenic in humans despite having robust affinity at 5-HT_{2A} and other serotonin receptors. Several theories have been advanced, but recent work combining molecular-biological and behavioral techniques is argued to have resolved the mystery and demonstrated important new mechanisms governing the actions of hallucinogenic drugs such as LSD. Specifically, comparisons of lisuride and other non-hallucinogenic compounds (such as ergotamine) with LSD and other hallucinogens (such as psilocybin and mescaline) in cell cultures, mutated animals and behavioral paradigms indicate that these drug classes exhibit functional selectivity at 5-HT_{2A} receptors [54]. Thus, LSD-like hallucinogens might regulate specific signaling mechanisms within cortical pyramidal cells that are not altered by lisuride, even though both LSD and lisuride function at the same 5-HT_{2A} receptors on these pyramidal cells. This example of functional selectivity as a potential mechanism underlying some actions of subclasses of 5-HT_{2A}-receptor agonists might open the door to novel treatment approaches for some of the aspects of schizophrenia that have, to date, been unresponsive to existing antipsychotic drugs, including both negative and cognitive symptoms.

The new possibilities indicated by functional selectivity mechanisms could revitalize the study of the neurobiology of serotonin and its relevance to the group of schizophrenia disorders. One next step toward this goal has already been reported. As noted earlier, converging lines of evidence indicate that the effects of hallucinogens mediated primarily by 5-HT_{2A} receptors are expressed via interactions with multiple other neuronal systems, notably including glutamatergic, dopaminergic and noradrenergic pathways. Extending substantial pharmacological and behavioral evidence for functional interactions between 5-HT_{2A} and metabotropic glutamate subtype 2 ($mGlu_2$) receptors [55], new findings indicate the possibility that such interactions might even occur at the level of the cell membrane. Specifically, studies [56] have now indicated that the $mGlu_2$ and 5-HT_{2A} receptors might be co-localized on cortical neurons and that activation of the $mGlu_2$ component of this receptor complex eliminates the hallucinogen-specific signaling normally produced by LSD via as-yet-unknown mechanisms. If confirmed, this finding would further support the idea that these cortical pyramidal cells are involved in the same gating of sensory, and perhaps cognitive, processes that are disrupted in schizophrenia and related psychoses. It is particularly intriguing, therefore, that a recently reported clinical trial has indicated that a prodrug for an agonist at $mGlu_2$ and $mGlu_3$ receptors seems to be efficacious in the treatment of positive psychotic symptoms of schizophrenia [57]. If confirmed in more extensive trials, this observation will signal an unexpected convergence of serotonergic and glutamatergic models of psychosis derived from the study of hallucinogenic drugs.

Future research on serotonergic contributions to psychoses

Six decades of discovery, observation and experimental study have generated compelling evidence that serotonergic systems and particularly central 5-HT_{2A} receptors are important in the genesis of drug-induced psychotic states and in the treatment and potentially the etiology of some psychotic disorders such as schizophrenia. The chemical tools of discovery provided by the late Albert Hofmann facilitated the elucidation of this fundamental relationship between serotonin and psychosis. Research to date, however, has left some questions unanswered and engendered many new questions. The serotonergic system contributes to psychotic states only by interacting with other neurotransmitter systems in the brain (Figure 2). The systems neuroscientists of the future will seek to understand the interactive dynamics associated with these profound alterations of perception and consciousness. Furthermore, serotonergic systems are undoubtedly important in the modulation of cognitive and affective functions that have not been discussed here but that are intrinsic to schizophrenia and related psychiatric disorders. As evidenced by recent new insights into underlying mechanisms, the field of serotonin research remains an exciting opportunity for discovery.

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