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A review of genetic alterations in the serotonin pathway and their correlation with psychotic diseases and response to atypical antipsychotics

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ABSTRACT

Serotonin is a neurotransmitter that plays a predominant role in mood regulation. The importance of the serotonin pathway in controlling behavior and mental status is well recognized. All the serotonin elements - serotonin receptors, serotonin transporter, tryptophan hydroxylase and monoamine oxidase proteins - can show alterations in terms of mRNA or protein levels and protein sequence, in schizophrenia and bipolar disorder. Additionally, when examining the genes sequences of all serotonin elements, several single nucleotide polymorphisms (SNPs) have been found to be more prevalent in schizophrenic or bipolar patients than in healthy individuals. Several of these alterations have been associated either with different phenotypes between patients and healthy individuals or with the response of psychiatric patients to the treatment with atypical antipsychotics. The complex pattern of genetic diversity within the serotonin pathway hampers efforts to identify the key variations contributing to an individual's susceptibility to the disease. In this review article, we summarize all genetic alterations found across the serotonin pathway, we provide information on whether and how they affect schizophrenia or bipolar disorder phenotypes, and, on the contribution of familial relationships on their detection frequencies. Furthermore, we provide evidence on whether and how specific gene polymorphisms affect the outcome of schizophrenic or bipolar patients of different ethnic groups, in response to treatment with atypical antipsychotics. All data are discussed thoroughly, providing prospective for future studies.

1. Introduction

Serotonin (or 5-hydroxytryptophan, 5-HT) is a neurotransmitter that regulates several functions, including dopamine release, cognitive function, memory, learning, vascular tone, appetite, coagulation, immune function, arousal, sexual desire (Pucadyil et al., 2005). Serotonin signaling in the brain bridges environmental stimulations to nuclear events through cAMP and CREB and activates the expression of many genes to produce proteins required for neuronal growth and long-lasting structural changes (Kandel, 2001). Serotonin signaling interacts, functionally, with dopamine signaling, as well as other neurotransmitters such as glutamate, acetylcholine, γ-aminobutiric acid (GABA).

In view of its important role in so many physiological processes, the serotonergic system has been implicated in the pathogenesis of psychiatric disorders, including the two major psychotic diseases, schizophrenia (SZ) and bipolar disorder (BD). SZ affects 1% of the general population. It is characterized by positive symptoms (delusions, hallucinations, disorganized thought, etc), negative symptoms (apathy, avolition, anhedonia, etc), and cognitive impairment (in working memory, sustained attention, etc) (Jones and McCreary, 2008). BD affects 1–4% of the population (Geddes and Miklowitz, 2013) and has four different subtypes (Phillips and Kupfer, 2013). It is characterized mainly by mania, hypomania, depression, rapid speech, increased locomotion and cognitive dysfunction (Craddock and Sklar, 2013; Hayden and Nurnberger, 2006). Several dysfunctions of the serotonin pathway occurring at the molecular-signaling-neuronal firing level in several brain regions have been correlated with both diseases. Furthermore, several genome wide association studies and/or copy number variation studies have investigated correlations between individual genes and psycho-pathogenesis and provided strong support for shared genetic risk across the diseases (Hayden and Nurnberger, 2006; Craddock and Sklar, 2013; Giusti-Rodríguez and Sullivan, 2013).

The dysfunction of serotonin pathway was potentially linked with SZ phenotype, when lysergic acid diethylamide (LSD), mescalin and psilocybin were observed that could cause various symptoms resembling SZ (such as hallucinations, altered cognition, delusions, paranoia) in

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healthy individuals (reviewed by Abi-Dargham, 2007). At the same time, particular atypical antipsychotic drugs (AAPs) were shown to modulate the levels of extracellular serotonin which affects their efficiency in improving positive and negative symptoms or cognition (Meltzer et al., 2003). Later on, the AAPs were found that had superior antipsychotic properties compared to typical antipsychotic drugs (APDs), a characteristic that was attributed mainly to their higher affinities for the serotonin receptor type 2 (5-HT2A) than for dopamine D2 receptors (Richtand et al., 2008). Thus, 5-HT2A receptors were firstly proposed to be involved in the pathophysiology of SZ and mood disorders (Serretti et al., 2007). The polymorphisms of the 5-HT2A gene became subject of many studies, some of which showed functional consequences for patients (Williams et al., 1996; Abdolmaleky et al., 2004; Ghadirivasfi et al., 2011). Meanwhile, numerous studies followed, which tested for associations between the polymorphisms of all serotonin elements (genes and proteins) and the major psychotic disorders.

In this review article, we summarize all genetic alterations found across the serotonin pathway (mRNA and protein levels, protein sequences and the single nucleotide polymorphisms, SNPs). We present data on whether and how these alterations correlate with the development and symptomatology of SZ or BD and, we deduce information from family studies on the contribution of familial relationships on the preferential transmission of these genetic variations. Finally, we provide evidence on whether and how specific gene polymorphisms affect the outcome of the psychotic disease, in response to treatment with AAPs, of schizophrenic or bipolar patients, of different ethnic groups. All data are discussed thoroughly, providing prospective for future studies.

2. Methods

PubMed and MEDLINE constituted the search engines for this review. The search terms consisted of "serotonin receptors and schizophrenia", "serotonin receptors and bipolar", "serotonin receptors and SNP", "antipsychotics and SNP", "SERT and schizophrenia", "SERT and bipolar", "TPH and schizophrenia", "TPH and bipolar", "MAO and schizophrenia", "MAO and bipolar", "SERT and SNP", "TPH and SNP", "MAO

Table 1
Alterations of the serotonin pathway elements detected by imaging or postmortem studies in SZ or BP patients, in various human brain areas.

Element (study)	Disease	Alterations	Brain areas	References
HTR1A				
(*PM*)	SZ	↑ Binding	Prefrontal cortex, cingulate/motor cortices, dentate gyrus	Selvaraj et al. (2014), Abi-Dargham (2007), Joyce et al. (1993)
		~ Binding	Dentate gyrus, amygdala, cingulum, motor cortex, occipital cortex, putamen, caudate, nucleus accumbens	Scarr et al. (2004), Joyce et al. (1993), Hashimoto et al. (1991)
		~ mRNA	Dorsolateral prefrontal cortex, hippocampus, etc	López-Figueroa et al. (2004), Burnet et al. (1996)
		↓ mRNA	Dentate gyrus	López-Figueroa et al. (2004)
	BP	↓ mRNA	Dorsolateral prefrontal cortex	López-Figueroa et al. (2004)
(*PET*)	SZ	↑ Binding	Left and right medial temporal cortex	Tauscher et al. (2002)
		↓ Binding	Amygdala	Yasuno et al. (2004)
		~ Binding	Several brain regions	Selvaraj et al. (2014)
	BP	↑ Binding	Raphe nuclei, hippocampus, dorsolateral prefrontal cortex, amygdala, etc.	Sullivan et al. (2009)
		↓ Binding	Anterior cingulate cortex, anterior insula, left parietal cortex, mesiotemporal cortices	Nugent et al. (2013), Drevets et al. (2007)
HTR1B				
(*PM*)	BP, SZ	↑ mRNA	Hippocampus	López-Figueroa et al. (2004)
	SZ	~ mRNA	Dorsolateral prefrontal cortex	López-Figueroa et al. (2004)
HTR1D				
(*PM*)	SZ	~ Binding	Dorsolateral prefrontal cortex, hippocampus	Dean et al. (2006), Scarr et al. (2004)
HTR1F				
(*PM*)	SZ	↓ Binding	Hippocampus	Scarr et al. (2004)
		~ Binding	Prefrontal cortex	Dean et al. (2006)
HTR2A				
(*PM*)	SZ	↓ Binding	Prefrontal cortex, frontal lobe, hippocampus	Selvaraj et al. (2014), Abdolmaleky et al. (2011), Scarr et al. (2004), Dean et al. (1999a)
		↑ Binding	Frontal cortex, striatum including the caudate	Selvaraj et al. (2014), Muguruza et al. (2013)
		~ mRNA	Dorsolateral prefrontal cortex	López-Figueroa et al. (2004)
	SZ, BP	↓ mRNA	Hippocampus	López-Figueroa et al. (2004)
	BP	↓ mRNA	Dorsolateral prefrontal cortex	López-Figueroa et al. (2004)
HTR2C				
(*PM*)	SZ	↓ mRNA	Prefrontal cortex	Castensson et al. (2003)
HTR4				
(*PM*)	SZ	~ Binding	Prefrontal cortex, hippocampus	Scarr et al. (2004), Dean et al. (1999b)
HTR6				
(*PM*)	SZ	↓ mRNA	Hippocampus	East et al. (2002a)
		~ mRNA	Dorsolateral prefrontal cortex	East et al. (2002a)
		~ Binding	Dorsolateral prefrontal cortex	East et al. (2002b)
HTR7				
(*PM*)	SZ	↓ mRNA	Prefrontal cortex	East et al. (2002a)
		~ mRNA	Hippocampus	East et al. (2002a)
		↓ Binding	Prefrontal cortex (BA9)	Dean et al. (2006)
SERT				
(*PM*)	SZ	↓ mRNA	Frontal lobe	Abdolmaleky et al. (2014)
		↓ Affinity	Hippocampus	Selvaraj et al. (2014), Naylor et al. (1996)
		↓ Binding	Prefrontal cortex	Selvaraj et al. (2014)
		~ Binding	Prefrontal cortex, caudate nucleus	Selvaraj et al. (2014), Dean et al. (1995)
TPH2				
(*PM*)	BP	↑ mRNA	Dorsolateral prefrontal cortex	De Luca et al. (2005)
MAOB				
(*PM*)	SZ	↑ mRNA	Prefrontal cortex	Castensson et al. (2003)

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