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Decreased serotonin$_{2C}$ receptor responses in male patients with schizophrenia

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ABSTRACT

Serotonin (5-HT)$_{2C}$ receptors in brain affect psychosis, reward, substance abuse, anxiety, other behaviors, appetite, body temperature, and other physiological measures. They also have been implicated in antipsychotic drug efficacy and side effects. We previously reported that the hyperthermia following administration of MK-212, a predominantly 5-HT$_{2C}$ receptor agonist, was diminished in a small sample of patients with schizophrenia (SCH), suggesting decreased 5-HT$_{2C}$ receptor responsiveness. We have now studied the responses to oral MK-212 and placebo in a larger sample of unmedicated male SCH ($n=69$) and normal controls (CON) ($n=33$), and assessed the influence of comorbid substance abuse (SA) on oral body temperature, behavioral responses, etc. The placebo-adjusted oral body temperature response to MK-212 was significantly lower in SCH compared to CON and not significantly different between the SCH with or without SA. Some behavioral responses to MK-212, e.g. self-rated feelings of increased anxiety, depression and decreased calmness, or good overall feeling, were significantly lower in the SCH patients compared to CON. These results add to the evidence for diminished 5-HT$_{2C}$ receptor responsiveness in SCH patients compared to CON and are consistent with reported association of HTR2C polymorphisms, leading to decreased expression or function of the HTR2C in patients with SCH.

1. Introduction

Serotonin (5-HT) has long been implicated in the pathophysiology and treatment of schizophrenia, beginning with the endogenous indole hallucinogen hypothesis (Rosengarten and Friedhoff, 1976), followed by numerous reports of altered 5-HT synthesis and metabolism, abnormalities in the levels of brain 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors, editing of 5-HT$_{2C}$ receptors, and coding or expression abnormalities in genes involved in the synthesis, metabolism and response to indoles and other compounds derived from tryptophan, the precursor of 5-HT (Bleich et al., 1988; Tang et al., 2014). The extensive and powerful mutual influences of 5-HT and dopamine (DA), two of the most important neurotransmitters required for reality testing, cognition, mood, motor function, and regulation of core body functions, such as energy expenditure, circadian rhythms, and endocrine function on the activity of each, led, in part, to an explicit 5-HT-DA hypothesis of schizophrenia (Meltzer et al., 1989; Meltzer and Nash,1991; van Veelen and Kahn, 1999; Beaulieu, 2012; Carli and Invernizzi, 2014). Thus, it was suggested that the effect of 5-HT at various 5-HT receptors on the release and response to DA, was a crucial component of the superiority of clozapine to typical antipsychotic drugs for a variety of aspects of schizophrenia, including psychosis, without extrapyramidal side effects and eventually suicide and cognition (Meltzer et al., 1989; Meltzer and Huang, 2008). While the emphasis was initially on 5-HT$_{2A}$ receptors, other 5-HT receptors, including the 5-HT$_{1A}$, 5-HT$_{2C}$, and 5-HT$_{7}$ receptors, were subsequently implicated in the treatment and pathophysiology of schizophrenia through their actions on cholinergic, noradrenergic, glutamatergic and GABAergic neurons, as well as DA neurons (Meltzer and Huang, 2008; Meltzer et al., 2012). It is of interest that selective 5-HT$_{2A}$ inverse agonists, e.g. pimavanserin and SR43459B, have been shown to be effective in acutely psychotic schizophrenia patients as augmentation of atypical antipsychotic drugs, or stand alone treatments (Meltzer et al., 2004, 2012a, 2012b). Many other 5-HT-related treatments for schizophrenia are in development, e.g. 5-HT$_{2C}$ agonists, (to be reviewed). Because of the heterogeneity of schizophrenia and the overlap of specific type of symptoms of schizophrenia with those of other neuropsychiatric disorders, including bipolar disorder, fronto-temporal dementia, and Alzheimer's disease, it is likely that only subgroups of

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patients who meet criteria for schizophrenia will manifest specific type of genetic and epigenetic 5-HT abnormalities and respond to serotonergic treatments (e.g. Iwamoto et al., 2009; Tang et al., 2014) We have previously reported on a subgroup of schizophrenic patients with abnormal responses to 5-HT_{2C} receptor stimulation (Lee et al. 1992). The expression of 5-HT_{2C} receptors has been reported to be markedly decreased in the prefrontal cortices of unmedicated (Castensson et al., 2003; Iwamoto et al., 2004) or medicated (Castensson et al., 2005) patients with SCH at the time of death, based on mRNA levels, although there is one non-replication (Dracheva et al., 2003).

The serotonin (5-HT)$_{2C}$ receptor is one of 13 5-HT G-protein coupled receptors and is highly expressed throughout the brain, including on cell bodies or terminals of cortical, and limbic pyramidal glutamatergic neurons and γ-aminobutyric acid (GABA) interneurons (Eberle-Wang et al., 1997; Berg et al., 2008; Labonte et al., 2009; Bubar et al., 2011). 5-HT_{2C} receptors are also present on cell bodies of ventral tegmental and nigro-striatal dopamine (DA) and acetylcholine (ACh) neurons, which is the basis for a major impact of 5-HT on reality testing, cognition, motor function, reward and substance abuse (Di Matteo et al., 2002; Bonsi et al., 2007; Berg et al., 2008). Stimulation of 5-HT_{2C} receptors in the ventral tegmenum decreases dopamine (DA) release in the nucleus accumbens (Di Giovanni et al., 2000; Berg et al., 2008), which contributes to their efficacy in treating psychotic symptoms in patients with schizophrenia (SCH) (Rosenzweig-Lipson et al., 2012). On the other hand, stimulation of 5-HT_{2C} receptor also decreases DA release in the cortex (Millan et al.1998), which might have an adverse effect on some types of cognition by decreasing DA-dependent signaling that is crucial for working memory (Meltzer and Huang, 2008; Huang et al., 2011). Some atypical antipsychotic drugs, e.g. clozapine, olanzapine, risperidone, and sertindole, are potent inverse agonists of 5-HT_{2C} receptors, indicating blockade of its constitutive activity, whereas others, e.g. lurasidone, quetiapine, and aripiprazole, have weak direct effects on 5-HT_{2C} receptors but still affect them through increasing DA release (Meltzer and Huang, 2008). Some typical antipsychotic drugs, e.g. chlorpromazine, thioridazine, spiperone, and thiothixene, are 5-HT_{2C} neutral antagonists (Rauser et al., 2001; Kroeze et al., 2003).

While 5-HT_{2A} receptor agonism has been shown to have a major role in the action of hallucinogens, e.g. 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) and D-lysergic acid diethylamide (LSD), 5-HT_{2C} agonism may alsocontributess to the psychotomimetic action of DOI (Canal et al., 2010). Nevertheless, other 5-HT_{2C} receptor agonists, because of functional selectivity (Moya et al. 2007), lack psychotomimetic properties, and also show antipsychotic drug-like action in animal models of psychosis, such as amphetamine-induced locomotor activity and pre-pulse inhibition (Marquis et al., 2007; Siuciak et al., 2007). The 5-HT_{2C} agonist, vabicaserin, has been reported to have an antipsychotic effect in patients with SCH (Rosenzweig-Lipson et al., 2012). In addition, 6-chlor-2[1-piperazinyl]-pyrazine (MK-212), a predominantly 5-HT_{2C} agonist, has been reported to cause anxiety when injected in the ventral hippocampus (Alves et al., 2004). Stimulation of 5-HT_{2C} receptors in the basolateral amygdala increases anxiety (Zangrossi and Graeff, 2014).

Furthermore, 5-HT_{2C} receptors have been shown to be involved in substance abuse, most likely based upon their ability to suppress mesocorticolimbic DA neurotransmissions (Pentkowski et al., 2010; Filip et al., 2012 Cunningham et al., 2013). Preclinical studies suggest 5-HT_{2C} agonists may be beneficial for the treatment of cocaine craving and relapse (Pentkowski et al., 2010; Filip et al., 2012; Cunningham et al., 2013). Furthermore, the cys23ser single nucleotide polymorphism (SNP) of the 5-HT_{2C} receptor gene has been reported to affect attentional bias to cocaine cues in patients with cocaine dependence (Anastasio, et al., 2014). Parallel to sharing neurochemical mechanisms involved in SCH and substance abuse, the rate of comorbid substance use disorders in patients with SCH has been reported to be significantly higher than the general population (Reiger et al., 1990; Hartz et al., 2014).

5-HT_{2C} agonists increase body temperature in man (Lee et al., 1992) and laboratory animals (Gudelsky et al., 1986; Hayashi et al., 2004). Furthermore, 5-HT_{2C} receptors are involved in feeding behavior (Hayashi et al., 2005). 5-HT_{2C} receptors in pro-opiomelanocortin neurons regulate energy and glucose homeostasis (Berglund et al., 2013). We reported that the oral body temperature increase following administration of MK-212 was markedly decreased in a substantial proportion of a sample of male and female patients with SCH ($n=23$) compared to normal controls (CON) ($n=22$) (Lee et al., 1992), as well as in male patients with cocaine use disorder ($n=10$) compared to male CON ($n=28$) (Lee and Meltzer, 1994). Therefore it was of interest to determine the relationship between the decreased oral body temperature response in patients with SCH and comorbid substance abuse.

MK-212 was shown to behave as a functionally selective 5-HT_{2C} agonist, as indicated by its ability to suppress cortical DA efflux only in 5-HT_{2A} knockout mice (Huang et al., 2011). MK-212 also increased cortical acetylcholine efflux via a 5-HT_{2C} agonist mechanism (Nair and Gudelsky, 2004). 5-HT_{2A} agonism is also the basis for stimulating corticosterone secretion in the rat by MK-212 (Hemrick-Luecke and Fuller, 1996).

The primary purpose of this study was to obtain additional information about the comparative effect of MK-212 on oral body temperature, endocrine and behavioral responses in male patients with SCH following MK-212. We also examined whether the responses to MK-212 were related to comorbid substance abuse.

2. Methods

2.1. Subjects

Sixty nine male patients [mean age: 33.7 ± 6.9(S.D.) years; range: 21–61 years] meeting DSM-IV criteria (APA, 1994) for SCH or schizoaffective disorder were studied. Diagnosis was established on the basis of the Schedule for Affective Disorder and Schizophrenia Lifetime (SADS-L) and Change (SADS-C) versions (Endicott and Spitzer, 1978). Thirty-nine patients had no history of substance abuse (SCH-NSA) and 30 patients had current or past history of substance abuse (SCH-SA) (mostly alcohol and/or cocaine). Thirty-three male CON [mean age: 28.6 ± 7.4 years; range:19–46 years], who did not have any psychiatric illness or substance abuse in themselves, based on interview with SADS-L (Endicott and Spitzer, 1978), and their first-degree relatives were studied. Twenty male patients and 11 male CON included in the prior study, which reported the decreased oral body temperature response to MK-212 in male and female SCH (Lee et al., 1992), were included in this study, as the prior study did not examine impact of substance abuse on oral body temperature responses to MK-212. All subjects were screened for any significant medical, neurological, neuroendocrine conditions and substance abuse problems by history, physical examination and comprehensive blood and urine tests, including urine drug screen. Also, height and weight were measured to assess the effect of body mass index [BMI: weight (kg)/height $(m)^2$] on the responses to MK-212.

Demographic and clinical data on patients with SCH and CON are presented in Table 1. Patients were psychotropic drug-free (e.g. haloperidol, fluphenazine, etc.) for at least 7 days before MK-212 or placebo administration, either because of self-withdrawal prior to admission to the study or in order to participate in the studies. No patient had received a depot neuroleptic within two cycles of their administration schedule to facilitate unmedicated status. Patients with substance abuse were required free of substance abuse at least 3 months prior to entering to the study. Patients were closely monitored with supportive care during the psychotropic drug-free period to detect early signs of deterioration, and to provide an appropriate clinical care after withdrawing patients from the study.

This protocol was approved by Institutional Review Board of the University Hospital of Cleveland. Written informed consents were obtained from all patients after complete explanation of the protocol before admission to the study.

2.2. Psychopathology assessment

Severity of psychopathology was evaluated at baseline by using Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) (0–6 scales), and BPRS total,