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Decrease in olfactory and taste receptor expression in the dorsolateral prefrontal cortex in chronic schizophrenia

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ABSTRACT

We have recently identified up- or down-regulation of the olfactory (OR) and taste (TASR) chemoreceptors in the human cortex in several neurodegenerative diseases, raising the possibility of a general deregulation of these genes in neuropsychiatric disorders. In this study, we explore the possible deregulation of OR and TASR gene expression in the dorsolateral prefrontal cortex in schizophrenia. We used quantitative polymerase chain reaction on extracts from *postmortem* dorsolateral prefrontal cortex of subjects with chronic schizophrenia ($n = 15$) compared to control individuals ($n = 14$). Negative symptoms were evaluated premortem by the Positive and Negative Syndrome and the Clinical Global Impression Schizophrenia Scales. We report that ORs and TASRs are deregulated in the dorsolateral prefrontal cortex in schizophrenia. Seven out of eleven ORs and four out of six TASRs were down-regulated in schizophrenia, the most prominent changes of which were found in genes from the 11p15.4 locus. The expression did not associate with negative symptom clinical scores or the duration of the illness. However, most ORs and all TASRs inversely associated with the daily chlorpromazine dose. This study identifies for the first time a decrease in brain ORs and TASRs in schizophrenia, a neuropsychiatric disease not linked to abnormal protein aggregates, suggesting that the deregulation of these receptors is associated with altered cognition of these disorders. In addition, the influence of antipsychotics on the expression of ORs and TASRs in schizophrenia suggests that these receptors could be involved in the mechanism of action or side effects of antipsychotics.

1. Introduction

Ectopic expression of olfactory and taste receptors (ORs and TASRs, respectively) has been described in several organs and tissues (Behrens and Meyerhof, 2010; Branscomb et al., 2000; De la Cruz et al., 2009; Feldmesser et al., 2006; Li, 2013; Parmentier et al., 1992; Vanderhaeghen et al., 1997; Xu et al., 2013; Yamamoto and Ishimaru, 2013; Zhang et al., 2007). Their function in these locations is not known in most cases but it has been proposed that both ORs and TASRs play particular roles in autocrine, paracrine and endocrine signaling (Aggio et al., 2012; Deshpande et al., 2010; Dreyer, 1998; Fukuda et al., 2004; Griffin et al., 2009; Kang and Koo, 2012; Kinnamon, 2012; Spehr et al., 2003, 2004). A variety of compounds, mostly of unknown origin and function, can bind to autocrine receptors on the same cell, neighboring cells or distant cells. More recently, ORs and TASRs, and their down-stream effectors have been identified in the rodent and human brain (Dehkordi et al., 2012; Garcia-Esparcia et al., 2013; Grison et al., 2014; Otaki et al., 2004; Singh et al., 2011), with a widespread distribution although with regional variations (Garcia-Esparcia et al., 2013). Moreover, ORs are functional—at least those

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expressed in dopaminergic cultured cells—in the presence of selective odorant molecules (Grison et al., 2014). About 400 ORs and dozens of TASRs are putatively expressed in the brain and ganglia of the autonomic nervous system (Glusman et al., 2001; Malnic et al., 2004; Niimura and Nei, 2005; Zhang et al., 2007; Zozulya et al., 2001), suggesting that they have substantial brain functions in physiological conditions (Barnea et al., 2004; Feinstein et al., 2004; Feinstein and Mombaerts, 2004; Otaki et al., 2004; Weber et al., 2002). Interestingly, ORs and TASRs are deregulated, at least in the frontal cortex and *substantia nigra*, in Parkinson's disease, the frontal cortex and entorhinal cortex in Alzheimer's disease and progressive supranuclear palsy, and the frontal cortex and cerebellum in Creutzfeldt-Jakob disease (Ansoleaga et al., 2013; Garcia-Esparcia et al., 2013). Deregulation is not merely result of neuron loss characteristic of these neurodegenerative diseases, as some ORs and TASRs are down-regulated or up-regulated in a disease-specific manner (Ansoleaga et al., 2013; Garcia-Esparcia et al., 2013). Moreover, deregulation of ORs has also been found in APP/PS1 transgenic mice bearing the Swedish APP mutation and PS1 deletion, which are used as a model for Alzheimer's disease (Ansoleaga et al., 2013). Although all these diseases have disorders in olfaction, mainly characterized by the loss of sense of smell, and in some of them the loss of taste to bitter substances (even that taste is rarely examined in neurodegenerative diseases), the mechanisms leading to loss of olfaction and taste have been attributed to the presence of abnormal protein deposits in the olfactory epithelium, olfactory bulb and tract, and to the abnormal innervation of primary and secondary olfactory and taste centers (Attems et al., 2014; Doty, 2003, 2012).

Schizophrenia (SZ) is a severe mental disorder affecting around 0.5–1% of the world adult population (Tandon et al., 2008). This disease constitutes a complex disorder with great variability in the manifestation of positive, negative and cognitive symptoms. Negative symptoms (i.e. lack of volition, poor or absent social functioning, blunted affect) and cognitive impairments (i.e. deficits in executive functions and working memory) are the core symptoms of schizophrenia and are the most persistent manifestations of the disease (Gold, 2004; Stahl and Buckley, 2007; Tandon et al., 2009). The dorsolateral prefrontal cortex (DLPFC) is involved these cognitive deficits (Frith and Dolan, 1996; Lewis and Moghaddam, 2006; Teffer and Semendeferi, 2012) and negative symptoms (Semkovska et al., 2001; Toda and Abi-Dargham, 2007). A dysfunction in this region has been widely described in functional and structural imaging studies and in many molecular reports (English et al., 2011; Goldstein et al., 1999; Konradi, 2005; Wong and Van Tol, 2003).

Altered olfactory functions have been reported in schizophrenia and their origin has been associated with altered secondary olfactory centers and also linked to altered olfactory bulb volume (Auster et al., 2014; Cohen et al., 2012; Kayser et al., 2013; Moberg et al., 2006; Nguyen et al., 2011, 2010; Rupp, 2010; Schneider et al., 2007). Hypoactivity and hypometabolism in frontal regions has been reported in SZ patients with olfactory agnosia (inability to recognize odors) or during olfactory identification, supporting a role of the frontal lobe in olfactory dysfunction in schizophrenia (Clark et al., 1991; Malaspina et al., 1998). The most severe and consistent dysfunctions reported in SZ patients were impaired odor identification and discrimination, implicating prefrontal neural compromise, while milder deficits of olfactory acuity or sensitivity, also reported in SZ, reflects a peripheral impairment of the olfactory system (Brewer and Pantelis, 2010; Cohen et al., 2012; Moberg et al., 1999; Rupp, 2010). In fact, electrical depolarization of the olfactory receptor neurons following stimulation with different doses and durations of hydrogen sulfide, a pure olfactory nerve stimulant, resulted in altered electric patterns, also supporting a primary olfactory receptor neuron dysfunction in schizophrenia (Turetsky et al., 2009). Regarding taste perception, there is no general agreement about the nature of taste disorders in schizophrenia, at least regarding the inability to taste the bitter chemical phenylthiocarbamide (Compton et al., 2007, 2013; Moberg et al., 2012; Moberg et al., 2007). Nothing is known about the expression of ORs and TASRs in the brains of patients suffering from schizophrenia. For this reason, the present study was designed to gain information about possible deregulation of OR and TASR expression in the dorsolateral prefrontal cortex in schizophrenia.

2. Material and methods

2.1. Brain tissue samples

A summary of the demographic, clinical and tissue-related features of the samples used for mRNA studies is shown in Table 1. *Postmortem* human brain tissue from the dorsolateral prefrontal cortex of subjects with chronic schizophrenia ($n = 15$) and control subjects with no history of psychiatric episodes ($n = 14$) were obtained from the collection of neurologic tissues of Parc Sanitari *Sant Joan de Déu* (Roca et al., 2008) and the Institute of Neuropathology Brain Bank (HUB-ICO-IDIBELL Biobank) following the guidelines of Spanish legislation and the approval of the local ethics committees. The study was approved by the institutional ethics committees. Written informed consent was obtained from each subject. We matched schizophrenia and control groups by gender, age, *postmortem* delay and brain pH. Table 1 shows the demographic, clinical and tissue-related characteristics of the samples. Schizophrenia subjects were institutionalized donors with long duration of the illness (Table 1) who had no history of neurological episodes. Experienced clinical examiners interviewed each donor *antemortem* to confirm the diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental

Table 1
Demographic, clinical and tissue-related features of cases ($n = 29$).

	Schizophrenia ($n = 15$)	Non-psychiatric controls ($n = 14$)	Statistic	p value
Gender	Male- 100% ($n = 15$)	Male- 100% ($n = 14$)	N/A	N/A
Age at death	75 ± 11 years	71 ± 8 years	1.09; 27	0.2863
PMD	4.6 ± 2.5 h	5.7 ± 1.9 h	1.38; 27	0.1797
pH	6.87 ± 0.27	6.74 ± 0.54	0.82; 27	0.4216
RIN	7.53 ± 0.63	7.74 ± 0.63	0.86; 27	0.3960
Age of onset of illness	26 ± 10 years	N/A	N/A	N/A
Duration of illness	49 ± 11 years	N/A	N/A	N/A
Daily AP dose[a]	380.67 ± 361.98 mg/day	N/A	N/A	N/A
Clinical Scales		N/A	N/A	N/A
PANSS	($n = 10$)			
Positive	23.90 ± 7.14			
Negative	26.60 ± 6.77			
General	50.50 ± 9.07			
CGI-SCH	($n = 13$)			
Positive	4.54 ± 2.31			
Negative	4.92 ± 2.22			
Depressive	2.23 ± 1.21			
Cognitive	4.46 ± 1.92			

Mean ± standard deviation or relative frequency are shown for each variable; PMD, *postmortem* delay; RIN, RNA integrity number; AP, antipsychotic; PANSS, Positive and Negative Syndrome Scale; CGI-SCH, Clinical Global Impression-Schizophrenia Scale; N/A, not applicable. All deaths were due to natural causes. T-statistic and degrees of freedom are shown for parametric variables.

[a] Last chlorpromazine equivalent dose was calculated based on the electronic records of drug prescriptions of the patients.