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The separate and combined effects of monoamine oxidase A inhibition and nicotine on the mismatch negativity event related potential☆

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ABSTRACT

The mismatch negativity (MMN) auditory event-related potential (ERP) has been extensively studied as a potential biomarker for abnormal auditory processing in schizophrenia (SZ), a population which exhibits abnormally high smoking rates. The relationship between nicotinic activation and cognition in SZ may be related to underlying nicotinic and NMDA receptor dysfunction within the disease. However, transient cognitive improvements via smoking in patients may also result from monoamine oxidase (MAO) inhibition, achieved through tobacco smoke. In 24 healthy non-smoking males, we investigated the separate and combined effects of nicotine and MAO-A inhibition via moclobemide (75 mg) on the optimal-5 variation of the MMN paradigm. No significant drug effects were observed in our total sample, however, stratification of individuals into low (N = 12) and high (N = 12) baseline MMN amplitude groups revealed increases in duration MMN amplitude relative to placebo by nicotine, as well as moclobemide, but not after the combination of the two. Because previous research has shown there was no effect of monoamine modulation on MMN, this study shows an unexpected effect of moclobemide on duration MMN.

1. Introduction

The high prevalence of tobacco smoking behavior among schizophrenia (SZ) patients (Lawrence et al., 2009) has been proposed to result from patients' need to counteract core cognitive deficits associated with nicotinic acetylcholine receptor (nAChR) dysfunction in SZ (Kumari and Postma, 2005). While a number of studies have investigated nicotine's effect on cognitive processing in SZ (Evans and Drobes, 2009; Gehricke et al., 2007; Kumari and Postma, 2005; Leonard et al., 2007; Ochoa and Lasalde-Dominicci, 2007; Wing et al., 2012; Winterer, 2010), including deficits in the auditory mismatch negativity (MMN) event-related potential (ERP) (Javitt et al., 1995; Inami et al., 2007), it is not known if the monoamine oxidase (MAO) inhibiting agents in tobacco smoke (Herraiz and Chaparro, 2005) also affect early auditory cognitive processing such as that indexed by the MMN.

SZ is associated with a number of behavioral abnormalities, including positive (e.g., hallucinations and delusions) and negative (e.g., flattened affect and anhedonia) symptoms, as well as deficits of cognition thought to be core to the disorder (Elvevag and Goldberg, 2000). Cognitive deficits arise prior to psychosis (Caspi et al., 2003), are largely resistant to medications (Hill et al., 2010), and are associated with functional outcome (Green et al., 2000). These findings have led to a focus on cognition-improving strategies for SZ patients, including the NIMH-MATRICS initiative (Marder, 2006), in hopes of developing treatments which promote functional outcome and recovery.

While smoking is strongly associated with addiction and addiction-related effects (Jasinska et al., 2013), there is evidence that nicotine has pro-cognitive effects in certain domains, including working memory and executive functioning (Swan and Lessov-Schlaggar, 2007). These have been theorized to result from nicotine's actions on nicotinic

Abbreviations: MMN, mismatch negativity; ERP, event-related potential; SZ, schizophrenia; MAO, monoamine oxidase; nAChR, nicotinic acetylcholine receptor; GABA, γ-aminobutyric acid; NMDAR, N-methyl-D-aspartate receptor; PCP, phencyclidine; 5-HT, serotonin; D1, dopamine receptor 1; D2, dopamine receptor 2; ATD, acute tryptophan depletion; BMI, body mass index; SSRI, selective serotonin reuptake inhibitor; DSM, diagnostic and statistical manual of mental disorders; SCID-NP, structured clinical interview for DSM-IV-R non-patient edition; FIGS, family interview for genetics studies; PP, placebo/placebo; MP, moclobemie/placebo; PNic, placebo/nicotine; MNic, moclobemide/nicotine; DHPG, 2,5-dihydroxyphenylglycine; CO, carbon monoxide; VEOG, vertical electrooculogram; HEOG, horizontal electrooculogram.

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acetylcholine receptors, and specifically, the α7 nAChR located on GABAergic interneurons of key structures, such as the prefrontal cortex, hippocampus, thalamus and ventral tegmental area (Mansvelder et al., 2006).

Nicotine's effects at the α7 nAChR may be particularly important in SZ, where there is evidence of receptor dysfunction in patients (Young and Geyer, 2013). The locus containing CHRNA7, the gene which encodes the α7 nAChR, has been linked to high risk for schizophrenia in genome-wide association studies (Stefansson et al., 2008). This gene has also been associated with deficient P50 suppression, an ERP-indexed measure of auditory sensory gating known to be abnormal in SZ (Freedman et al., 1997). Post-mortem studies have found reductions in α7 nAChR protein binding in the prefrontal cortex (Martin-Ruiz et al., 2003), cingulate cortex (Marutle et al., 2001), thalamic reticular nucleus (Court et al., 2000), and hippocampus (Freedman et al., 1995). The relatively low sensitivity to nicotine exhibited by the α7 nAChR (compared to the higher sensitivity exhibited by the α4β2 receptor) might explain the unique smoking behavior of SZ patients, who have been shown to extract more nicotine per cigarette on average than non-SZ smokers (Olincy et al., 1997).

Recently, primate studies have shown α7 nAChR stimulation to be essential for the normal functioning of glutamatergic N-methyl-D-aspartate receptor (NMDAR) mediated working memory circuits in the dorsolateral prefrontal cortex (Yang et al., 2013). Sub-chronic administration of phencyclidine (PCP), an NMDAR antagonist, reduced the binding of a selective nAChR radioligand ([^{11}C]CHIBA-1001) in the frontal cortex of rhesus monkeys (Hashimoto et al., 2008). In SZ, NMDA receptor hypofunction has been proposed as central to the pathophysiology of the disease (Javitt et al., 2012). NMDAR antagonists, such as ketamine, mimic symptoms of SZ in healthy volunteers, including positive, negative, and cognitive symptoms (Lahti et al., 2001). Modern pathophysiological models of SZ include NMDA dysfunction in neural structures such as the hippocampus (Lodge and Grace, 2011) and thalamus (Clinton and Meador-Woodruff, 2004) with dopamine irregularities arising as a downstream effect.

Importantly, the effect of smoking on the modulation of dopamine and other monoamines is not a purely nicotinic phenomenon. It has been established that chronic smoking can inhibit both isoforms of MAO; MAO-A by ~28% (Fowler et al., 1996a) and MAO-B by ~40% (Fowler et al., 1996b) through the actions of β-carboline alkaloids in tobacco smoke (Herraiz and Chaparro, 2005). MAO-A may be of particular importance to the cognitive effects of chronic smoking due to its selectivity for oxidation of serotonin and noradrenaline, as well as its oxidative actions on dopamine, which it shares with MAO-B as a non-selective substrate (Finberg, 2014). It was previously shown that selective pharmacological inhibition of MAO-A, when combined with acute nicotine via chewing gum, improves P50 sensory gating in healthy, non-smoking males (Smith et al., 2015) and these effects are more pronounced in individuals with low baseline gating. However, it is not known whether this effect extends to other sensory and cognitive processes, such as MMN-indexed sensory memory.

MMN, in its basic form, is an index of auditory change detection, typically measured as a scalp-recorded auditory ERP proceeding a "deviant" tone within a train of standard tones (Näätänen et al., 2007), and is thought to represent sensory memory encoding in the brain. The "optimal" MMN paradigm (Näätänen et al., 2004) involves a series of short standard tone "pips" interspersed with 5 types of deviant tones comprised of variants (in relation to the standard) in duration, frequency (pitch), intensity (loudness), aural location, as well as a "gap" deviant created by eliminating sound from the middle portion of the standard tone. MMN, and particularly the duration deviant, has been well documented as deficient in SZ (see Näätänen and Kähkönen, 2009 for review) and this deficit has been hypothesized to result in part from NMDAR dysfunction due to observations that NMDA antagonists block MMN generation in primates without affecting primary auditory processing (Javitt et al., 1996). Interestingly, duration MMN specifically has been shown to predict conversion to psychosis in at-risk individuals (Näätänen et al., 2015), supporting laboratory modulation of MMN as a useful model for preliminary research into the cognitive deficits underlying SZ.

The effects of nicotine on MMN have been investigated in a number of studies. Nicotine improved MMN in smokers by increasing amplitude to the standard tone in a roving paradigm utilizing continuously changing stimuli (Baldeweg et al., 2006), and improved MMN to an interstimulus interval deviant in both smokers and non-smokers (Martin et al., 2009). In a consonant–vowel variation of the MMN paradigm, nicotine increased MMN amplitudes in smokers and non-smokers (Harkrider and Hedrick, 2005). Nicotine delivered via patch shortened latencies to a frequency deviant but did not affect amplitude (Inami et al., 2005). A selective agonist of the α4β2 nAChR increased amplitude and reduced latency to frequency deviants in non-smokers (Dunbar et al., 2007). Overall, it seems that nicotine in the absence of monoaminergic modulation can affect MMN, however, because of varying methods and heterogeneous samples, often combining smokers and non-smokers, few of the studies to date are directly comparable, and no attempts have yet been made to separately elucidate the effects of nicotine and MAO inhibition on MMN.

The effect of MAO inhibition on MMN is not known, however, modulation of MAO-A substrates such as dopamine, serotonin, and norepinephrine and their effects on MMN have been studied using a variety of methods in healthy individuals. Haloperidol, a dopamine D2 receptor antagonist, increased MMN amplitudes to frequency deviants (Kähkönen et al., 2001), but failed to alter MMN in later studies (Kähkönen et al., 2002) with one study finding no effect of haloperidol on either frequency or duration MMN (Pekkonen et al., 2002). Dopamine receptor activation via D_1 agonist bromocriptine, and D_1/D_2 agonist pergolide (Leung et al., 2007) both had no effect on duration MMN. Methylphenidate, a dopamine and norepinephrine reuptake inhibitor, had no effect on MMN frequency or duration (Korostenskaja et al., 2008). Acute tryptophan depletion (ATD), a method of decreasing serotonin synthesis, has increased MMN amplitudes to duration and frequency deviants (Kähkönen et al., 2005), however, a more recent study found no effect of ATD on MMN (Leung et al., 2010). Escitalopram, a selective serotonin reuptake inhibitor (SSRI) increased amplitude to frequency MMN at moderate (Oranje et al., 2008) and high doses (Wienberg et al., 2009). 5-HT_{2A} receptor activation via psilocybin had no effect on frequency or duration MMN (Umbricht et al., 2002, 2003). Norepinephrine increase via atipamezole, an alpha$_2$ receptor antagonist also had no effect on MMN (Mervaala et al., 1993) nor did growth hormone response measurements to apomorphine and clonidine neuroendocrine challenge tests, measurements of dopamine and norepinephrine system activation, respectively (Hansenne et al., 2003).

The consistent modulation of MMN by nicotine as opposed to monoamines in the studies described above may result from enhanced presynaptic NMDAR mediated synaptic plasticity facilitated through activation of nAChRs (Lin et al., 2010). Enhanced cholinergic transmission via galantamine administration has been shown to modulate MMN (Moran et al., 2013) by increasing sensitivity to "bottom-up" processing of auditory input, thereby enhancing response to deviants (Todd et al., 2013). These findings also further support the theory that smoking SZ patients suffering from potential NMDAR dysfunction may achieve cognitive benefits preferentially from the nicotinic components of tobacco smoke and not its MAO inhibiting properties.

The objective of the present study was to determine the separate and combined effects of nicotine and MAO-A inhibition on MMN, while avoiding confounding effects of clinical and/or smoking status. Taken together, previous studies seem to suggest that nicotine can affect MMN while modulation of MAO-A substrates does not. Therefore, we hypothesized that pharmacological inhibition of MAO-A would not affect nicotine's ability to improve MMN in a group of healthy non-smokers. It has previously been observed that nicotine fails to alter frequency MMN in a group of smokers (Knott et al., 2006) who would