Neuroscience 166 (2010) 145–156

EFFECTS OF NICOTINE ON THE AMPLITUDE AND GATING OF THE AUDITORY P50 AND ITS INFLUENCE BY DOPAMINE D2 RECEPTOR GENE POLYMORPHISM

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Abstract—Evidence of normalized auditory P50 suppression with acute nicotine in schizophrenia has supported the contention that elevated smoking rates in this disorder may be an attempt to correct a nicotinic receptor pathophysiology that may underly impaired sensory gating in these patients. There is very little information regarding the neurochemical or genetic pathways through which nicotine regulates P50 amplitude and its suppression in human studies. In a randomized, double-blind, placebo-controlled design with 24 non-smokers, this study examined the influence of TaqIA dopamine D2 receptor gene polymorphisms on P50 and its inhibition during nicotine gum (6 mg) administration. Within a paired click (S_1-S_2) paradigm, placebo treated A1$^+$ and A1$^-$ allele groups differed with respect to P50 amplitude and gating. While nicotine (relative to placebo) attenuated S_1 P50 amplitude in A1$^+$ allele carriers, in the A1$^-$ carriers it increased S_2 P50 amplitude and increased P50 gating as indexed by an augmented gating difference wave (GDW). These findings suggest that nicotine exerts mixed gating properties in healthy nicotine naive volunteers and that dopamine functions to alter both P50 and its gating as well as their response to acute nicotine agonist treatment. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: nicotinic receptors, acetylcholine, dopamine receptor gene, middle latency auditory event-related potentials, non-smokers, schizophrenia.

The increased prevalence of smoking reported in schizophrenia patients (~50%–80%) compared to the normal population (~20%) has generally been interpreted as self-treatment of pathophysiological core features associated with an underlying vulnerability to the disease (Diaz et al., 2008). Smoking may also be an attempt buffer psychotropic drug side effects or to augment the therapeutic effects of antipsychotics in order to improve behavioural and/or cognitive deficits associated with this disorder (Dalack et al., 1998; Kumari and Postma, 2005). There is growing evidence from human laboratory studies of non-abstaining smokers and non-smokers that nicotine can exert facilitative effects on cognitive processing (Evans and Drobes, 2009; Gehricke et al., 2007), particularly in the attentional domain where acute nicotine administration has been shown to improve aspects of attention dysfunction in schizophrenia (AhnAllen et al., 2008; Levin et al., 1996; Smith et al., 2002), with the effects being shown to be greater in patients than in controls (Barr et al., 2008).

Improvements in attentional-cognitive processing have been attributed in part to nicotine's ability to filter out irrelevant stimuli (Kassel, 1997), a gating mechanism which is purported to be deficient in schizophrenia and is evidenced electrophysiologically in the form of aberrant inhibition of P50, a middle latency auditory event-related brain potential (MLAERP). Typically observed in a paired auditory stimulus (click) paradigm where the first (S_1) of the closely (<1000 ms) paired clicks (presented at long [8–10 s] inter-pair intervals) is said to activate excitatory pathways and initiate or "condition" inhibitory processes in the brain, and the second click (S_2), which is thought to predominantly activate the inhibitory pathways (due in part to the conditioning of the pathways by the S_1 stimulus), "tests" the strength of inhibition, this elementary deficit in auditory sensory gating is indexed by the amplitude suppression of the electroencephalographically (EEG)-derived vertex (C_z) positive MLAERP at ~50 ms (P50) post-S_2 stimulus. Reflected as the ratio of S_2 to S_1 P50 amplitude [rP50] or as the subtractive difference [dP50] between S_2 and S_1 amplitude values, P50 suppression is typically robust at ~55% (i.e. S_2/S_1 gating ratio ~.45) in healthy controls while in unmedicated patients with schizophrenia, suppression is approximately 20% (i.e., S_2/S_1 ratio ~.80) (Bramon et al., 2004; De Wilde et al., 2007; Freedman et al., 1987, 1991, 1997; Light and Braff, 1999; Myles-Worsley et al., 1996; Patterson et al., 2008; Potter et al., 2006; Thaker, 2008). Although described as a failure to inhibit the S_2 response, there is also evidence that this P50 suppression deficit may be a reflection of an attenuated S_1 amplitude without any further reduction of the S_2-elicited P50, resulting in a profile of equal amplitude for S_1 and S_2 in schizophrenia

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Abbreviations: $\alpha 4\ \beta_2$ nAChR, alpha 4 beta 2 nicotinic acetylcholine receptor; CHRNA7, alpha 7-nicotinic acetylcholine receptor subunit gene; COMT, catechol-O-methyl transferase; D2, dopamine D2 receptor; DIS, Disinhibition Scale of the SSS-V; dP50, P50 difference score index of sensory gating; DRD2 A1$^-$, A1$^-$ allele of the dopamine D2 receptor gene; DRD2 A1$^+$, A1$^+$ allele of the dopamine D2 receptor gene; DRD2 TaqIA, TaqIA polymorphism of the dopamine D2 receptor gene; DRD2, dopamine D2 receptor gene; EEG, electroencephalogram; EPQ, Eysenck Personality Questionnaire; ES, experience seeking scale of the SSS-V; GDW, gating difference wave; MLAERP, middle latency auditory event-related potential; PET, positron emission tomography; PFC, prefrontal cortex; rP50, P50 ratio index of sensory gating; SPL, sound pressure level; SSS-V, Sensation Seeking Scale-V; α7-nAChR, alpha 7 nicotinic acetylcholine receptor.

0306-4522/10 $ - see front matter
doi:10.1016/j.neuroscience.2009.11.053

(Freedman et al., 1983; Jin et al., 1997; Clementz and Blumenfeld, 2001). While the left and right superior temporal gyri and the primary auditory cortex have been linked to P50 elicitation, P50 suppression has been associated with activity in reticular, thalamic, hippocampal, and rhinal regions, as well as in frontal cortical areas (Grunwald et al., 2003; Korzyukov et al., 2007; Knott et al., 2009a; Mayer et al., 2009; Mears et al., 2006).

Gum-administered and smoke-inhaled nicotine have been shown to normalize P50 sensory gating in unaffected family members and in medicated patients, respectively (Adler et al., 1992, 1993). Cholinergic mechanisms are believed to play a key role in this facilitated inhibition as acute nicotine activates and desensitizes low (α7) nicotine affinity nicotinic acetylcholine subunit receptors (nAChRs) (Picciotto et al., 2008) and chronic smoking/long-term nicotine exposure upregulates hippocampal nAChRs (Marks et al., 1983; Schwartz and Kellar, 1983; Benwell et al., 1988), which act to regulate sensory gating (Freedman et al., 1996) and are expressed at reduced levels in schizophrenia postmortem brains (Freedman et al., 1995; Court et al., 1999). That the incidence of heavy smoking in schizophrenia can be interpreted as an attempt to self-correct an α7 nAChR based P50 pathophysiologic mechanism (De Luca et al., 2004), is supported through genetic linkage analysis in families of schizophrenia patients, where polymorphisms of the α7-nAChR subunit gene (CHRNA7) have been linked to the capacity to inhibit P50 (Freedman et al., 1997, 2001, 2002, 2003; Leonard et al., 1998, 2002; Myles-Worsley et al., 1999), acting both as a risk and a protective factor for sensory gating deficits (Hovy et al., 2004; Raux et al., 2002). In the DBA/2 mouse strain with a knockdown for CHRNA7 that is also associated with a significantly reduced expression of hippocampal α7-nAChRs, P50 sensory gating is diminished compared to gating in a control (C3H) mouse strain (Stevens et al., 1996, 1998).

Direct evidence for a cholinergically mediated P50 gating mechanism is found with the nAChR partial agonists DMXB-A (also known as GTS-21) and topisetron, which increased P50 inhibition in patients with schizophrenia (Koike et al., 2005; Olincy et al., 2006). DMXB-A (Simosky et al., 2002; Stevens et al., 1998), clozapine (Simosky et al., 2003) and the selective partial nAChR α7 agonist JN403 (Feverbach et al., 2009) were also found to restore P20/N40 MLAERP deficits (the hippocampal-recorded rodent analogues of the human P50) in DBA/2 mice via stimulation of α7-nAChRs. Although initial studies observed no correlation between P50 gating and high affinity (α4 β_2) nAChRs (Stevens et al., 1996), α4 β_2-nAChR stimulation has since been shown to contribute to the facilitating effects of nicotine in the DBA/2 and C57BL/6J (the latter, like schizophrenia, exhibiting small MLAERP amplitudes) mouse models of sensory gating (Phillips et al., 2007). The facilitated P20/N40 gating seen in infrahumans with nAChR agonists and nicotine have varied with respect to the involvement of S_1 and S_2, with some studies showing increases in S_1 and decreases in S_2 (Stevens et al., 1996; Stevens and Wear, 1997), while others have shown cholinergically mediated gating to be accomplished primarily through an increase in the S_1 response with less change to the S_2 (Metzger et al., 2007; Radek et al., 2006). The P50 normalizing effect of atypical (vs. typical) antipsychotics, being most prominent with clozapine and with minimal or no effect being observed with olanzapine and risperidone (Adler et al., 2004; Light et al., 2000; Nagamoto et al., 1996, 1999), has also been attributed to their affinity to nAChRs (Light and Braff, 2003).

nAChRs are distributed in a variety of brain structures relevant to sensory processing, such as the hippocampus and sensory cortices (Patterson and Nordberg, 2000) and they have been demonstrated to influence the release not only of acetylcholine but a number of other neurotransmitters implicated in cognitive functions, such as dopamine, norepinephrine, serotonin, GABA and glutamate (Benowitz, 2008). The degree to which these non-cholinergic neurotransmitter systems are involved in the nicotine-improved gating effect is as yet unknown. In addition to the cholinergic hippocampal pathway, dopamine neurotransmission in the PFC, the dysregulation of which is involved in the pathophysiology of schizophrenia (Amar et al., 2008; Davis et al., 1991; Goto and Grace, 2007; Howes and Kapur, 2009; Murray et al., 2008), has been implicated in the gating of MLAERPs (Grunwald et al., 2003; Knight et al., 1999; Light et al., 1999; Waldo et al., 1994), most likely via cortical signal-to-noise modulation by PFC dopamine (Winterer and Weinberger, 2004). In a model of hippocampal gating, evidence of reduced absolute S_1 P50 and S_2 P50 amplitudes in schizophrenia has been interpreted as a separate deficit from the lack of sensory gating, with the amplitude reduction being linked to disturbed dopamine neurotransmission and, more specifically, to a dopamine excess (Moxon et al., 2003a,b). Accordingly, traditional neuroleptic medications like haloperidol, a dopamine (D2) receptor antagonist, that block the action of both dopamine and norepinephrine, have been shown to increase S_1 and S_2 amplitudes in patients without improving sensory gating (Freedman et al., 1983; Baker et al., 1987; Adler et al., 1992; Nagamoto et al., 1996).

In healthy controls, both the dopamine precursor L-dopa and the dopamine (D2) agonist bromocriptine reduced S_1 and S_2 amplitudes but did not affect P50 gating (Oranje et al., 2004) and in rats, the dopamine receptor agonist quinpirole improved both hippocampal (N40) and cortical (N35) measures of P50 suppression through a decrease of S_1 amplitude, with the cortical but not the hippocampal effects being antagonized by haloperidol (De Bruin et al., 2001). Acute challenge with amphetamine, a dopamine and norepinephrine releaser, reduced gating in healthy controls (Light et al., 1999) and both gating and N40 amplitudes in rats, with gating being normalized with dopamine (D1) antagonism (Stevens and Wear, 1997) while both gating and amplitude reductions were normalized by haloperidol (Adler et al., 1986; Bickford-Wimer et al., 1990). Norepinephrine depletion on the other hand only reversed the disruption by amphetamine on gating and did not affect amphetamine-attenuated MLAERP amplitudes (Adler et al., 1988). That dopaminergic gating