Pharmacological intervention and abstinence in smokers undergoing cessation treatment: A psychophysiological study

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ABSTRACT

As a composite concept, negative affect comprises various aversive emotional experiences, such as irritability and nervousness. It is a critical motivational factor that helps maintain smoking behavior, and contributes significantly to smoking cessation failure as a core withdrawal symptom. Prior research has indicated an important role of nicotinic mechanisms in negative affect processing. The most effective smoking cessation medication, varenicline, targets nicotinic acetylcholine receptors (nAChRs) as a partial agonist, while another first-line cessation medication, bupropion, has shown antagonistic effects on nAChRs. Therefore, it is possible that both medications work to reduce smoking behavior through modulating negative affect processing. To evaluate this hypothesis, we examined the impact of varenicline tartrate and bupropion hydrochloride sustained-release on electrophysiological responses to affective, cigarette-related, and neutral cues before and during smoking cessation treatment in a randomized placebo-controlled clinical trial. The participants were 206 smokers, a subset of 294 participants that were enrolled in a larger smoking cessation clinical trial who were randomly assigned to one medication group for 12 weeks. Orbicularis oculi (startle eyeblink response) and corrugator supercilii facial electromyographic (EMG) reactivity toward emotional pictures (i.e., pleasant and unpleasant) in a picture-viewing task were measured before treatment and 2 and 6 weeks after treatment was started. The startle and corrugator EMG activities increase with the exposure to unpleasant cues, and served as indices for negative emotional reactivity (NER). We found that after 6 weeks, drug reduced startle-related NER in the varenicline group, but not in the bupropion or placebo group. Independent of medication treatment, lower baseline NER, as measured by the corrugator EMG activity, predicted a higher likelihood of smoking abstinence 1 and 3 months after quitting smoking. These findings indicate the important roles of varenicline in negative affect processing and negative emotional reactivity in the course of smoking cessation.

1. Introduction

Varenicline tartrate (referred to as varenicline) and bupropion hydrochloride sustained-release (referred to as bupropion) have been recommended by the Food and Drug Administration as first-line pharmacotherapies for nicotine dependence in the United States (Fiore et al., 2008). Unfortunately, only about 14% treated with bupropion and 22% treated with varenicline maintain continuous abstinence throughout the first year (Cahill et al., 2012). Understanding these medications' therapeutic mechanisms can help researchers improve the treatment efficacy of these pharmacologic interventions.

Bupropion, as well as its active metabolite, (2S,3S)-hydroxybupropion, is a noncompetitive antagonist on nicotinic acetylcholine receptors (nAChRs), particularly those containing α4β2 and α3β2 subunits (Damaj et al., 2004; Carroll et al., 2014). It is also a dopaminergic and noradrenergic reuptake inhibitor (Stahl et al., 2004). Varenicline is a selective α4β2-containing nAChR partial agonist and a full agonist at the homomeric α7-containing nAChR (Aubin et al., 2014) and also exerts some antagonistic properties on these receptors with nicotine co-administration (Mihalak et al., 2006). Bupropion's nicotinic antagonism and varenicline's partial agonism on α4β2 nAChR have been suggested to be particularly important for their therapeutic effects (Aubin et al., 2014; Carroll et al., 2014). As nicotine's primary molecular targets, nAChRs mediate smoking's rewarding effects (Picciotto

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et al., 1998; Tapper et al., 2004) and withdrawal symptoms during nicotine deprivation (Salas et al., 2004).

Clinically, withdrawal symptoms are recognized as a major component of nicotine dependence (American Psychiatric Association, 2013). Among the various aspects of smoking withdrawal, negative affect is considered to be the core symptom (Baker et al., 2004). Broadly speaking, negative affect captures subjective distress and unpleasant engagement and is a general dimension that includes various aversive emotional experiences, such as irritability, fear, disgust, nervousness, contempt, guilt, and stress (Watson et al., 1988). Negative affect has been found to play an important role in precipitating smoking relapse. Smokers are more vulnerable to relapse if they have higher negative affect levels before they quit smoking (Ginsberg et al., 1995; Killen et al., 1996; Kenford et al., 2002; Cinciripini et al., 2003) or after they quit smoking (Kenford et al., 2002). Consistent with their superior therapeutic efficacies in improving smoking abstinence, both bupropion and varenicline reduce negative affect levels more than placebo (Gonzales et al., 2006; Jorenby et al., 2006; West et al., 2008; Cinciripini et al., 2013).

The reformulated negative reinforcement model of drug addiction (Baker et al., 2004), has provided a theoretic framework on elucidating the role of negative affect in drug addiction, particularly with nicotine dependence. As the key to continued nicotine use, control of negative affect begins with a preconscious level of processing of negative affect information — a signal of an incipient increase in negative affect levels. Repeated nicotine use and withdrawal lead smokers to be able to pre-consciously process this negative affect information by detecting its interoceptive cues during the early stages of nicotine withdrawal. By responding to this interoception, smokers self-administer nicotine to reduce negative affect and the increase of nicotine levels will reverse this early withdrawal process. The reduction of negative affect and other unpleasant withdrawal symptoms contributes to the reinforcement of smoking behavior and the development and maintenance of nicotine addiction. This negative reinforcement model of nicotine addiction suggests that understanding the biological processes associated with the early and preconscious stages of negative affect processing will help elucidate the relationship among nicotine use, nicotine withdrawal, and negative affect.

Many studies using rodent models and human neuroimaging technique have investigated nicotinic mechanisms in modulating various aspects of negative affect. Different classes of nAChR (e.g., α4β2, α7) are expressed widely in the brain, including the hippocampus, the ventral tegmental area, and the striatum, and stimulate and regulate the release of various types of neurotransmitters, including glutamate, GABA, dopamine, and serotonin (Dani and Bertrand, 2007). Local infusion and use of pharmacological agents (e.g., nicotine, nAChR antagonists) have suggested the importance of stress hormones, serotonergic, and GABAergic pathways in mediating nicotine's effect on anxiety-related behaviors using various behavioral paradigms (e.g., elevated plus maze testing) in rodents (Costall et al., 1989; Brioni et al., 1993; Cao et al., 1993; For more, see review by Picciotto et al., 2002). Genetic studies that involved evaluating polymorphism of the α4 subunit and β2 null mutation have found that these genetic variants modulate nicotine's effects on fear-related acoustic startle response in mice (Tritto et al., 2002; Owens et al., 2003).

Given that both bupropion (Damaj et al., 2004) and varenicline (Mihalak et al., 2006) target nAChRs, both should also be expected to play a role in regulating the activities of the above-mentioned nAChR-expressing brain regions and neurotransmitters that are regulated by nicotinic activities. This postulation is supported by several functional neuroimaging studies (Menossi et al., 2013). For example, compared with placebo, bupropion treatment reduced brain activation of the left ventral striatum when smokers were instructed to resist craving actively (Culbertson et al., 2011), and it also reduced smoking cue-related activation in the anterior cingulate cortex (Brody et al., 2004). Several neuroimaging studies found that varenicline treatment reduced the

blood oxygen level-dependent (BOLD) activity of the amygdala during a face emotion identification task (Loughead et al., 2011) and in the resting state (Franklin et al., 2011), and the resting state connectivity between amygdala and insula (Sutherland et al., 2013). Despite both medications modulating nAChR-expressing brain regions, it should be noted that bupropion and varenicline appear to be associated with different activation patterns (e.g., anterior cingulate cortex by bupropion vs. amygdala by varenicline), which suggests that bupropion and varenicline may have differential neurophysiological mechanisms. Importantly, research has consistently suggested that both the amygdala and anterior cingulate cortex play critical roles in fear and other emotional processing (Phelps and LeDoux, 2005; Mechias et al., 2010; Shackman et al., 2011). Thus, it can be expected that by regulating these affect-related brain regions, bupropion and varenicline should modulate emotional processing. However, this hypothesis has not been tested clinically.

Using psychophysiological approaches to study negative affect, one can measure immediate physiological changes in response to a negatively-valenced stimulus (Bylsma et al., 2008), which we refer to as negative emotional reactivity (NER). NER can be indexed by the startle eyeblink response, measured from the orbicularis oculi, and by corrugator supercilii electromyographic (EMG) activity using the picture-viewing paradigm (Bradley et al., 2001). The startle response itself is a reflexive reactivity to an abrupt aversive stimulus (e.g., loud noise), and basic research has extensively characterized its neural pathways (Davis et al., 1982; Koch and Schnitzler, 1997; Swerdlow and Geyer, 1999; Lang et al., 2000; Grillon and Baas, 2003). In addition, startle response can be modulated by presenting the startle stimulus within the context of a pre-existing ambient emotional cue, such as an unpleasant picture (e.g., gun threat), and the more unpleasant and arousing the ambient cue, the larger the startle response (Bradley et al., 2001), a paradigm that is termed affect-modulated startle response.

Corrugator activity represents outward facial expression when negative information is processed (Jäncke, 1996), as its EMG levels are significantly increased in response to unpleasant pictures, particularly mutilations and contamination, compared with neutral pictures, as opposed to the startle response, which is more sensitive to animal and human attack (Bradley et al., 2001). Although both startle and corrugator reactivity toward unpleasant stimuli can index NER, they may reflect different subdomains of negative affect processing (e.g., corrugator in disgust, such as in response to mutilations and contamination vs. startle in fear, such as in response to gun threat). In addition, they appear to involve differential brain regions (Lang et al., 2000; Lee et al., 2012). Thus, taken together, measuring NER using both startle response and corrugator reactivity methods will allow us to evaluate the differential effects of bupropion and varenicline on negative affect-related biological processes.

In this study, we used startle response and corrugator EMG measures to evaluate whether bupropion and varenicline reduced NER in smokers who were undergoing smoking cessation treatment. We examined whether medication and abstinence modulated these NER-related measures during the cessation course and further tested if baseline NER predicted abstinence status. Specifically, we hypothesized that: (1) treatment with bupropion and varenicline would result in lower levels of NER than placebo, (2) abstinence would be associated with lower levels of NER than nonabstinence during post-quit time points, and (3) smokers with lower NER at baseline time point would be more likely to remain abstinent after they quit smoking. In addition to these three primary hypotheses related to NER, we conducted secondary analyses to examine whether bupropion and varenicline treatment would modulate smoking cue-related startle response, given that previous research has indicated that smoking-related cues reduce startle response relative to neutral cues (Geier et al., 2000; Cinciripini et al., 2006; Dempsey et al., 2007; Rehme et al., 2009).