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Neurophysiological effects of modafinil on cue-exposure in cocaine dependence: A randomized placebo-controlled cross-over study using pharmacological fMRI☆

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ABSTRACT

Objective: Enhanced reactivity to substance related cues is a central characteristic of addiction and has been associated with increased activity in motivation, attention, and memory related brain circuits and with a higher probability of relapse. Modafinil was promising in the first clinical trials in cocaine dependence, and was able to reduce craving in addictive disorders. However, its mechanism of action remains to be elucidated. In this functional magnetic resonance imaging (fMRI) study therefore, cue reactivity in cocaine dependent patients was compared to cue reactivity in healthy controls (HCs) under modafinil and placebo conditions.
Methods: An fMRI cue reactivity study, with a double-blind, placebo-controlled cross-over challenge with a single dose of modafinil (200 mg) was employed in 13 treatment seeking cocaine dependent patients and 16 HCs.
Results: In the placebo condition, watching cocaine-related pictures (versus neutral pictures) resulted in higher brain activation in the medial frontal cortex, anterior cingulate cortex, angular gyrus, left orbitofrontal cortex, and ventral tegmental area (VTA) in the cocaine dependent group compared to HCs. However, in the modafinil condition, no differences in brain activation patterns were found between cocaine dependent patients and HCs. Group interactions revealed decreased activity in the VTA and increased activity in the right ACC and putamen in the modafinil condition relative to the placebo condition in cocaine dependent patients, whereas such changes were not present in healthy controls. Decreases in self-reported craving when watching cocaine-related cues after modafinil administration compared to the placebo condition were associated with modafinil-induced increases in ACC and putamen activation.
Conclusions: Enhanced cue reactivity in the cocaine dependent group compared to healthy controls was found in brain circuitries related to reward, motivation, and autobiographical memory processes. In cocaine dependent patients, these enhanced brain responses were attenuated by modafinil, mainly due to decreases in cue- reactivity in reward-related brain areas (VTA) and increases in cue reactivity in cognitive control areas (ACC). These modafinil-induced changes in brain activation in response to cocaine-related visual stimuli were associated with diminished self-reported craving. These findings imply that in cocaine dependent patients, modafinil, although mainly known as a cognitive enhancer, acts on both the motivational and the cognitive brain circuitry.

1. Introduction

Cocaine dependence is a substance use disorder with a chronic course for most patients and early treatment drop-out and relapse are common. Currently, there is no proven effective pharmacological treatment for cocaine dependence (Dackis & O'Brien, 2002; Penberthy, Ait-Daoud, Vaughan, & Fanning, 2010; van den Brink, 2011). Psychological treatments such as cognitive behavioral therapy are only moderately effective in cocaine dependence, with some evidence that adding contingency management further reduces cocaine use and related problems (Dutra et al., 2008; for reviews see Knapp, Soares, Farrel, & Lima, 2007). Cocaine is a stimulant that binds to the dopamine transporter and blocks dopamine reuptake resulting in increased levels of dopamine in the synapse and increased stimulation of the postsynaptic dopamine receptors in the nucleus accumbens, and thus activates the mesolimbic dopaminergic reward

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pathway, including the ventral tegmental area (VTA) and the ventral striatum (VS). In addition, cocaine binds to the norepinephrine transporter and serotonin transporter. As a result, recent quests for effective pharmacotherapy for cocaine dependence have included a wide range of medications, including dopamine agonists, serotonergic agents, and GABA-ergic medications, since GABA can suppress dopamine release in the striatum, thus indirectly blocking the rewarding effects of cocaine in the brain (van den Brink, 2011). In addition, studies have been conducted with a cocaine vaccine in an attempt to prevent cocaine from entering the brain (for a review see Shorter & Kosten, 2011).

Although several of these novel pharmacological interventions have shown promising results, the efficacy of these medications for the treatment of cocaine dependence has still to be established in large-scale double-blind placebo-controlled trials. In order to be more successful with future medication trials, we need a better understanding of the neurobiological effects of these medications in cocaine dependent patients.

One of the more promising pharmacological compounds that is currently tested in cocaine dependence is the cognitive enhancer modafinil (2-[(diphenylmethyl) sulfinyl] acetamide). Modafinil is a wakefulness-promoting drug which is registered for the treatment of narcolepsy, shift work sleep disorder, and obstructive sleep apnea syndrome. The exact mechanism of action of modafinil still has to be elucidated, but the available evidence suggests that modafinil binds to the dopamine, the serotonin and the norepinephrine transporters, increases the release of the excitatory neurotransmitter glutamate, and reduces GABA-ergic neurotransmission (Ballon & Feifel, 2006; Madras et al., 2006). Although these characteristics suggest that modafinil may act as a substitution for cocaine with the consequence of potential for abuse, modafinil did not result in increased euphoria or cocaine craving in a clinical trial in cocaine patients (Dackis et al., 2003) and has a low abuse potential, unlike amphetamine-like drugs (Jasinski, 2000; Jasinski & Kovacevic-Ristanovic, 2000). In addition, laboratory studies with modafinil have shown a lack of stimulant-like effects in cocaine abusers (Rush, Kelly, Hays, Baker, & Wooten, 2002; Vosburg, Hart, Haney, Rubin, & Foltin, 2010). Finally, pretreatment with modafinil decreased cocaine euphoria in a cocaine infusion study in cocaine abusers (Dackis et al., 2003).

Modafinil not only shows beneficial effects on cognitive functions such as memory and executive functioning in healthy individuals (Turner et al., 2003), but also in patients with schizophrenia (Scoriels et al., 2011; Spence, Green, Wilkinson, & Hunter, 2005; Turner, Clark, Pomarol-Clotet, et al., 2004) or attention deficit/hyperactivity disorder (Turner, 2006). Besides these general beneficial effects on cognitive functions, modafinil has been shown to diminish impulsivity in addictive disorders such as pathological gambling (Zack & Poulos, 2009) and metamphetamine dependence (Dean et al., 2011).

Treatment with modafinil has been employed in several cocaine dependent samples. Modafinil resulted in improved clinical outcome in the first double-blind placebo-controlled trial in 67 cocaine dependent patients, in which modafinil was combined with psychosocial treatment for cocaine dependence (Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005). The second double-blind placebo-controlled trial with modafinil in 210 cocaine dependent patients showed that modafinil reduced craving and reduced the number of days that cocaine was used in cocaine dependent patients, but only in those without a history of alcohol dependence (Anderson et al., 2009). However, very little is known about the neural mechanisms by which modafinil exerts its beneficial effects in patients with cocaine dependence. Reduced cue reactivity may be one of the mechanisms by which modafinil results in diminished craving (Anderson et al., 2009), but improved cognitive control over craving may be another potential mechanism of action. To date, only one study investigated the neural correlates of the beneficial effects of a single dose of modafinil on cognition in substance dependence (Ghahremani et al., 2011). In this study, modafinil improved learning by enhancing neural function in prefrontal brain regions in methamphetamine dependent patients. However, there are no data available on the neural mechanisms behind the addiction-related motivational and cognitive control effects of modafinil, including cue reactivity and craving.

Increased cue reactivity and heightened attention for addiction-related cues are important elements in the development of addictive behaviors (Goldstein & Volkow, 2002) and heightened cue reactivity can promote relapse in substance dependence (Cooney, Litt, Morse, Bauer, & Gaupp, 1997; Grusser et al., 2004; Kosten et al., 2006; Marissen et al., 2006). Neuroimaging studies of cue reactivity in addictive disorders have repeatedly reported increased activity in motivation related regions such as the striatum (including caudate nucleus and putamen), the ventral tegmental area (VTA), and the orbitofrontal cortex (OFC), in attention/control related regions such as the anterior cingulate cortex (ACC) and in memory related regions such as the parietal cortex (Daglish et al., 2001; David et al., 2005; Franklin et al., 2007; Goldstein et al., 2009; Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010; Grusser et al., 2004; Kilts et al., 2001; Kosten et al., 2006; McBride, Barrett, Kelly, Aw, & Dagher, 2006; Tapert, Brown, Baratta, & Brown, 2004).

Given the promising findings on modafinil as a treatment for cocaine dependence and the scarce knowledge of its effects on brain mechanisms involved in cue reactivity and craving, we decided to perform a functional magnetic resonance imaging (fMRI) study on cue reactivity in cocaine dependent patients employing modafinil and placebo using a single dose, double-blind, placebo cross-over design. We compared cue reactivity in cocaine dependent patients and healthy controls (HCs) under modafinil and placebo conditions. Based on the existing knowledge regarding the neurobiological mechanisms involved in cue reactivity we hypothesized that modafinil would exert its effects mainly through modifications in activation in the attentional, motivational, and autobiographical memory brain circuitries, specifically activation in the VTA, striatum (including caudate and putamen), ACC, OFC, and parietal cortex. In addition, we hypothesized that these modafinil-induced modifications in brain activation in the cocaine dependent group would be related to changes in their subjective craving.

2. Materials and methods

2.1. Participants

A total of 16 treatment seeking cocaine dependent patients and 18 HCs participated in the study. However, three cocaine dependent and two HCs had to be excluded from analysis for one of the following reasons: MRI data were not (fully) available due to due to scanner failure (N = 3), excessive head motion during scanning (N = 1) or scanner artefacts in functional images (N = 1). The remaining 13 cocaine dependent patients and 16 HCs were used in the statistical analyses. Cocaine dependent patients were recruited from a Dutch addiction treatment center, and were recently abstinent as indicated by self-report. In addition, abstinence was corroborated by current participation in this treatment program, in which the cocaine dependent patients all had participated for a minimum duration of three weeks (detoxification phase, followed by clinical treatment). HCs were recruited through advertisements in newspapers, through the internet and local bulletin boards and were matched on sex, education and age to the cocaine dependent patients. Exclusion criteria were: DSM-IV substance use disorders (other than cocaine and nicotine for the CD group and nicotine for the HC group); other current DSM-IV diagnoses (except for antisocial personality disorder in the cocaine dependent group); lifetime history of head injury with loss of consciousness for more than 5 min; neurological disorders; unstable medical condition; low level of education (school drop-out before age 16); use of medication affecting the central nervous system; MRI ineligibility due to non-removable metal objects or claustrophobia.