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Subjective, cognitive/psychomotor, and physiological effects of aripiprazole in Chinese light and heavy smokers

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ABSTRACT

Background: Drug addiction researchers have begun to study dopamine partial agonists as potential therapeutic agents. The partial dopamine D_2 receptor agonist aripiprazole has recently been tested as a treatment for stimulant and alcohol dependence in both animal and clinical studies.
Methods: A randomized and placebo-controlled pilot clinical study was conducted in a population of Chinese light and heavy smokers to assess the effect of aripiprazole on various responses to smoking. The primary outcomes were subject's ratings on questionnaires of smoking urge, withdrawal syndromes, and cigarette evaluation. Placebo, 5, and 10 mg aripiprazole were acutely administered in all participants, with administrations at least 7 days apart. Subjective responses to a smoked cigarette, working memory, and attention/psychomotor performance were assessed before and after drug administration in each experimental session. Abstinence-induced smoking urge, withdrawal symptoms, blood pressure, and heart rate were also measured every 45 min after drug administration. Finally, a cue-testing session was carried out 4 h after each drug administration.
Results: Administration of 10 mg aripiprazole significantly decreased both the subjective response and psychological reward derived from smoking a cigarette in heavy smokers. While neither 5 nor 10 mg aripiprazole significantly decreased abstinence-induced smoking urges or withdrawal symptoms in light and heavy smokers, these doses substantially attenuated drug cue-induced smoking urges in heavy smokers. Aripiprazole did not affect working memory or attention/psychomotor performance.
Conclusions: Light and heavy smokers responded differently to aripiprazole across various dependent measures. Aripiprazole may potentially affect various subjective responses to smoking in heavy smokers.

1. Introduction

China's increasing tobacco consumption stands out against the global decline in tobacco production and use. China now produces and consumes more tobacco than any other nation (van Liemt, 2002; Yang et al., 1999). This extensive tobacco use has resulted in unprecedented levels of nicotine dependence in China. Approximately 30 million Chinese citizens took up smoking between 1996 and 2002, increasing the population of Chinese smokers to more than 300 million (Yang et al., 1999), and over 60% of Chinese male adults smoke (Anderson Johnson et al., 2006; Yang et al., 2005). Nicotine dependence has caused profound public health, social and economic consequences; there are nearly one million tobacco-related deaths per year in China, a number expected to double or even triple by 2025 (Liu et al., 1998; Niu et al., 1998).

Researchers hoping to develop medications that could stem this public health crisis have focused on the neurobiology of nicotine dependence (Fagerstrom and Balfour, 2006; George and O'Malley, 2004; Le Foll and George, 2007; Lerman et al., 2007). Ample neurochemical (Grady et al., 2002; Imperato et al., 1986; Nisell et al., 1994), anatomical (Clarke and Pert, 1985; Clarke et al., 1984; Pich et al., 1997; Schwartz et al., 1984), and behavioral (Corrigall and Coen, 1994a,b; Ikemoto et al., 2006; Le Foll et al., 2002, 2003) evidence shows that the dopaminergic system (particularly D_2 receptors) plays a key role in the effects of nicotine. Thus, researchers have suggested using dopamine partial agonists as therapeutic agents (Childress and O'Brien, 2000; Ohlsen and Pilowsky, 2005; Pulvirenti and Koob, 1994, 2002). Furthermore, these drugs cause little behavioral disruption and lack reinforcing effects, suggesting that they

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may be effective pharmacotherapies for the treatment of drug abuse and dependence (Pilla et al., 1999; Platt et al., 2000; Sorensen et al., 2008). While behavioral profiles of dopamine partial agonists have been characterized mostly in animals treated with stimulants (Izzo et al., 2001; Orsini et al., 2001; Pilla et al., 1999; Platt et al., 2000; Pulvirenti and Koob, 1994), animal (Pich et al., 1997) and clinical (Fehr et al., 2008) studies have demonstrated that common neuronal substrates underlie the effects of both nicotine and other drug of abuse. These findings suggest that dopamine partial agonists could yield a novel pharmacological treatment for nicotine dependence.

The partial dopamine D_2 receptor agonist aripiprazole (Burris et al., 2002) may be particularly promising. Aripiprazole has high occupancy of dopamine D_2/D_3 receptors in human striatum and extrastriatal regions (Grunder et al., 2008), and is an effective antipsychotic, functioning via the stabilization of dopamine systems (McGavin and Goa, 2002). However, relatively few studies have examined the therapeutic utility of aripiprazole against drug dependence. In animal studies, acute administration of aripiprazole has been demonstrated to profoundly affect the psychomotor and reinforcing effects of cocaine (Feltenstein et al., 2007; Leite et al., 2008; Sorensen et al., 2008; Wee et al., 2007) and the acute motivational effects of amphetamine during the early stages of abstinence (Schwabe and Koch, 2007). Chronic administration of high doses of aripiprazole also substantially reduces alcohol, but not saccharin, consumption (Ingman et al., 2006). In clinical settings, the effects of aripiprazole have been investigated most extensively in alcohol dependent patients, with inconclusive results. Some clinical studies have found that aripiprazole mitigates alcohol use and its effects. For example, acute aripiprazole administration altered the euphoric and sedative effects of alcohol in healthy volunteers (Kranzler et al., 2008). Chronic aripiprazole treatment reduced compulsiveness (Martinotti et al., 2007) and increased abstinence from alcohol use (Janiri et al., 2007; Warsi et al., 2005). However, a recent multi-center double-blind study found that alcohol-dependent patients treated with aripiprazole (initiated at 2 mg/day and titrated to a maximum dose of 30 mg/day at day 28) dropped out of the trial at higher rates than those receiving placebo, possibly due to dose-related adverse events (Anton et al., 2008). While researchers have also studied the effects of aripiprazole on the use of other drugs of abuse, including amphetamine (Lile et al., 2005; Stoops, 2006; Stoops et al., 2006; Tiihonen et al., 2007), cocaine (Lile et al., 2008; Stoops et al., 2007), and ephedrine (Arnold and Yager, 2007), the potential therapeutic effects on drug dependence, including nicotine dependence, remains largely undetermined.

Thus, while preventing or attenuating relapse is a key challenge in treating drug dependence, and nicotine is one of the world's most popular drugs of abuse, only one case report has documented the effects of aripiprazole on nicotine dependence (Ramaswamy and Bhatia, 2006). In a patient that met DSM-IV criteria for nicotine dependence and alcohol abuse, with a history of major depressive disorder, administration of aripiprazole reduced the desire for smoking and resulted in eventual smoking abstinence (Ramaswamy and Bhatia, 2006). Here, we investigated the acute effects of aripiprazole on several key behavioral aspects of nicotine dependence in smokers: subjective response to a smoked cigarette, abstinence-induced smoking urge, withdrawal symptoms, and cue-induced responses. The evaluation of the effect of therapeutic agents on these abstinence- and drug cue-induced responses is critical to understand their efficacy, since craving levels are significantly associated with the likelihood of relapse in cigarette smokers (Bagot et al., 2007; Killen and Fortmann, 1997; Shiffman et al., 1997; Swan et al., 1996; Toll et al., 2007), and triggers of craving in cigarette smokers include abstinence from smoking and presentation of smoking-related cues (Drobes and Tiffany, 1997; Tiffany and Drobes, 1991). Since the physical and psychological responses to smoking have been shown to vary substantially with the level of nicotine dependence, it is also important to explore the effect of aripiprazole in light and heavy smokers (Payne et al., 1996; Brauer et al., 2001; Van Den Eijnden et al., 2003). Lastly, since China faces a growing nicotine addiction epidemic and because all previous clinical studies on aripiprazole were conducted in Europe and North America, a randomized and placebo-controlled clinical study was conducted exclusively in Chinese Han smokers.

2. Methods

2.1. Participants

Male smokers were recruited via word-of-mouth and were paid 250 RMB (approximately US$ 30) to participate. The inclusion criteria were as follows: (1) males, aged 21–45 years; (2) smoking 5–10 cigarettes/day and scoring <5 on the Fagersrom Test for Nicotine Dependence (FTND) for light smokers; or smoking ≥15 cigarettes/day continuously for at least 12 months prior to screening and scoring ≥6 on the FTND for heavy smokers; (3) afternoon end-exhaled carbon monoxide (CO) concentration ≥10 ppm (Bedfont Mini2 Smokerlyzer, Bedfont Scientific Ltd., Rochester, Kent, England); (4) general good health as determined by a physician. The exclusion criteria were as follows: (1) abuse of or dependence on other drugs (opioid and methamphetamine) based on self-report or positive urine test at either recruitment screening or testing; (2) current or past history of DSM-IV Axis I disorders; (3) current use of antidepressants or diagnosis of depression; (4) clinically evident cognitive impairment; or (5) self report of treatment with any prescription drug during the previous 2 weeks or with any over-the-counter drug during the 3 days prior to the experimental session. The study and consent form were approved by the Institutional Review Boards of Peking University Health Center, and the Beijing Hui-Long-Guan Hospital, Beijing, China. All participants provided written informed consent prior to participation.

A total of 85 smokers were screened for participation, 27 of whom enrolled and 20 of whom completed the study. The participants dropped out of the study mainly due to loss of contact. All were ethnically Han Chinese. Table 1 provides the means and standard deviations of the study population's basic demographics and smoking and drinking history. There were no significant differences between light and heavy smokers in these variables, except for the number of cigarettes smoked per day and score on the FTND (two-tailed, unpaired Student's t-test, $p < 0.05$).

2.2. Overview of the experimental procedure

This was a cross-over design in which each participant served as their own control. On the screening day, participants completed questionnaires assessing their basic demographics, nicotine/alcohol/illicit drug use, and medical and psychiatric history. The original questionnaires (in English) were translated into Chinese by two Chinese researchers who were also knowledgeable in the field of drug dependence. Several Chinese smokers with comparable age and education as our participants were asked to look at and circle any word they could not understand. The questionnaires were subsequently revised until the smoker panels passed all the questionnaires. Urine samples were collected and exhaled carbon monoxide (CO) was measured. Study physicians also examined potential participants. Eligible participants were scheduled for three experimental sessions at least 7 days (range 7–16) apart. Throughout the study, participants were instructed to abstain from any alcoholic beverages for 24 h prior to the experimental session. Participants were also asked to refrain from consuming caffeinated drinks or solid food the morning of each experimental session. On test day, participants were required to arrive no later than 8:30 am and experiments usually started at 9:00 am. Each participant provided a urine sample upon arrival and an exhaled air specimen to detect the presence of

Table 1
Participant characteristics.

Variable	Light smokers		Heavy smokers		p value
	Mean	SD	Mean	SD	
Number of participants	10	–	10	–	–
Age	29.40	2.07	30.10	1.64	0.79
Education (years)	11.00	0.92	10.40	0.62	0.59
Cigarettes/day	6.80	0.61	24.00	2.21	<0.01
Duration of smoking (years)	8.70	1.51	12.10	1.39	0.11
FTND scores	1.90	0.62	7.00	0.42	<0.01
Drinks/day	1.60	0.31	1.95	0.49	0.55
Drinking days/week	3.60	0.68	2.60	0.62	0.29