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Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 639 – 647
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

# Changes of smoking behavior and serum adrenocorticotropic hormone, cortisol, prolactin, and endogenous opioids levels in nicotine dependence after naltrexone treatment☆

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Accepted 6 April 2005
Available online 4 June 2005

**Abstract**

This study was done to evaluate the therapeutic effects of naltrexone on smoking behaviors and to measure the changing of brain substances for elucidating the mode of action by naltrexone. Twenty-five voluntarily participated healthy male smokers were randomly assigned to naltrexone group or placebo group for 2 weeks. In this study, naltrexone group showed significant reduction in daily cigarette consumption amount, the expiratory CO levels, brief questionnaire for smoking urge (B-QSU) score, and FTQ score. However, only 2 subjects in naltrexone group quitted smoking completely at 4th week. Plasma levels of pituitary hormones (ACTH, cortisol, and prolactin) and endogenous opioids (β-endorphin and dynorphin A) were checked weekly before and after the 'provocation and smoking coupled' stimulus once in a week for 3 weeks. In naltrexone group, pituitary hormones showed upward tendencies even though only the prolactin had statistical significance. However, β-endorphin and dynorphin A were not significantly different between the two groups. It was suggested that naltrexone made effects on hypothalamo–pituitary–adrenocortical axis activity as well as smoking behavior. However, the meaning of these endocrinal changes by naltrexone is not conclusive, whether it is beneficial or aversive.


*Keywords:* Endogenous opioid; Hypothalamo–pituitary–adrenocortical axis; Naltrexone; Nicotine dependence

## 1. Introduction

Nicotine derived from cigarette mimics the effects of acethylcholine at the nicotinic acethylcholinergic receptors (nAchR) in brain. These receptors are located on the site of diverse central presynaptic and postsynaptic cholinergic and non-cholinergic neurons especially in dopaminergic and opioidergic pathways (Rosecrans and Karin, 1998). Activation of the nAChR by smoking facilitates the release of dopamine into synaptic clefts in nucleus accumbens and subsequently makes physiological and molecular changes that result in nicotine dependence (Picciotto, 1998). In contrast with dopamine, the contribution of endogenous opioid to the development of nicotine dependence is still vague. Definitely, nicotine stimulates the pituitary release of the pro-opiomelanocortin (POMC) peptide group, which contains the precursor for β-endorphin. However, the elevation of β-endorphin levels was responded differently depending on the concentration of nicotine administered.

*Abbreviations:* ACTH, adrenocorticotropic hormone; B-QSU, Brief Questionnaire for Smoking Urge; CRF, corticotrophin-releasing factor; FTQ, Fagerstrom Tolerance Questionnaire; HPA axis, hypothalamo–pituitary–adrenocortical axis; nAchR, nicotinic acethylcholinergic receptors; POMC, pro-opiomelanocortin.

☆ This paper was received a poster award at 16th ECNP Congress (2003, Prague Czech Republic).

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doi:10.1016/j.pnpbp.2005.04.008

Studies using opioid antagonist to evaluate the reinforcing properties of endogenous opioids in nicotine dependence have yielded ambiguous results to date (Modesto-Lowe and Van Kirk, 2002). However, it is generally accepted that endogenous opioids in response to nicotine contribute to nicotine reinforcement to some extent. It is due to the dopamine–opioid interaction of dopaminergic neurons in ventral tegmental area tonically inhibited by neighboring GABAergic interneurons that express μ opioid receptors and are inhibited by morphine (Wise, 1998). Besides, κ opioid receptors are located on the dopaminergic axon terminals in nucleus accumbens and κ receptor ligands inhibit dopamine release into the synaptic cleft (Herz, 1998). Hahn et al. (2000) reported that activation of κ opioid receptors prevented nicotine-induced locomotor stimulation in rats, which suggested other possible linkages of endogenous opioids and nicotine self-administration.

Single exposure of nicotine enhances dopaminergic, serotonergic, GABAergic, and glutaminergic synaptic transmission (Rosecrans and Karin, 1998; Mansvelder et al., 2002) and leads elevation of circulating levels of cortisol, growth hormone, prolactin, and β-endorphin (Wilkins et al., 1982; Pomerleau et al., 1983; Seyler et al., 1986) but it desensitized readily (Sharp and Beyer, 1986). Therefore other explanations that resulted from experiments carried out in a more long-term period and targeted for on-going smoker are needed to understand chronic addicted states.

Koob and Le Moal (2001) defined drug addiction as an allostatic state in which vulnerability to relapse persists even after drug taking has ceased. They insisted that one of the main factors in forming this deviation of brain reward mechanism is the brain stress system. The increase of corticotrophin-releasing factor (CRF) after acute withdrawal activates the brain stress system and mediates the behavioral responses including re-administration. It means that not only the dopaminergic–opioidergic neural interaction but also the brain stress system could be the major element in habitual drug intake.

Stress influences the central amygdaloid nucleus and it leads following responses of adaptive behavior, autonomic nervous system, and neuroendocrine system through amygdalofugal CRF pathway (Rodriguez de Fonseca and Navarro, 1998; Stewart, 2003). It could be observed as activation of hypothalamo–pituitary–adrenal (HPA) axis, alternation of mood, and relapse to drug use. Smoking is sometimes precipitated by stress and stress also contributes to the reinforcing value of cigarette smoking. Increased sympathetic tone and cortisol levels additively after combinations of psychological stress and nicotine administration via smoking were reported sequentially (Pomerleau and Pomerleau, 1987, 1990). These results did not support the idea that nicotine protects against the adrenergic component of the stress response, as there was no reduction of stress-induced catecholamines when nicotine was administered. By these backgrounds, Pomerleau (1998) insisted the possibility that endogenous opioids contribute primary to nicotine reinforcement under special conditions such as stress. In this experiment, the subjects were scheduled to do sham smoking without real puff for 5 min. Subjects could regard the craving resulted from this provocation as a stressful situation because they were already in the nicotine abstinence at least for an hour.

Naltrexone is one of the non-specific opioid antagonists and it expands its application variable to substance abuse. However in some trials the benefits of naltrexone for smoking cessation were admitted but in others probable precipitation of withdrawal symptoms during abstinence by naltrexone was also presented (David et al., 2001). We, the authors, intended to re-evaluate the contribution of naltrexone on nicotine dependence treatment through this study. It was hypothesized that changes of these pituitary hormones or endogenous opioids might be involved in the outcomes of naltrexone treatment in smoking cessation. Plasma endogenous opioids (β-endorphin and dynorphin A) and stress related pituitary hormones (ACTH, cortisol, and prolactin) were measured to observe concomitant endocrinal alternation by naltrexone treatment in smokers. Furthermore, the responses of neurohormones and endogenous opioids listed above were checked before and after 'provocation-smoking' stimulus. It was done to shed light on the additional changes of the hormones and opioids during naltrexone treatment by usual smoking behavior in stressful situation. To obtain more actual results, study was designed in the manner of keeping subjects' ordinary lifestyle as possible as we could.

## 2. Methods

### 2.1. Recruitment of subjects

The subjects were voluntary participated healthy male smokers who wanted to quit smoking. After detailed explanations of study plan, we received informed consent. The severities of nicotine dependence were measured by Fagerstrom Tolerance Questionnaire (FTQ, Fagerstrom and Schneider, 1989). Subjects who scored below 4 were excluded. The subjects having either physical or mental disorders including other substance dependence by DSM-IV criteria (APA, 1994) were also excluded. Finally 25 subjects were recruited for this study. As a double-blind placebo-controlled method, 13 subjects were assigned to naltrexone group and 12 were assigned to a placebo group randomly.

### 2.2. Organization of the sessions and medications

Subjects were asked to visit at the starting point (baseline time-point), 1 week later (first week time-point), 2 weeks later (second week time-point), and 4 weeks later (forth week time-point). During the first 2 weeks naltrex-