Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2008 July 1; 32(5): 1131–1138. doi:10.1016/j.pnpbp.2007.12.012.

Tobacco/Nicotine and Endogenous Brain Opioids

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Abstract

Smoking is a major public health problem with devastating health consequences. Although many cigarette smokers are able to quit, equal numbers of others cannot! Standard medications to assist in smoking cessation, such as nicotine replacement therapies and bupropion, are ineffective in many remaining smokers. Recent developments in the neurobiology of nicotine dependence have identified several neurotransmitter systems that may contribute to the process of smoking maintenance and relapse. These include: especially dopamine, but also norepinephrine, 5-hydroxytryptamine, acetylcholine, endogenous opioids, *gamma*-aminobutyric acid (GABA), glutamate, and endocannabinoids. The present review examines the limited contribution of the endogenous opioid system to the complex effects of nicotine/tobacco smoking.

Keywords

Analgesia; Endogenous opioids; Nicotine; Reinforcement; Stress; Tobacco

1. Beyond the dopamine hypothesis of tobacco/nicotine reinforcement

There is no question that tobacco smoking has been one of the most potent and prevalent addictions influencing behavior of human beings for more than five centuries. After the discovery of the New World by Columbus and his crew, Spaniards who arrived in Yucatan found the Mayas ardent tobacco smokers. Maya artifacts now indicate that they smoked tobacco many centuries earlier. Current population studies indicate that in the U.S., approximately 23% of American smoke cigarettes. Approximately 430,000 people die each year as a result of smoking-attributable medical illness (George and O'Malley, 2004; Giovino, 2002). Despite success in the public health and legislative forefronts (WHO Framework Convention on Tobacco Control, 2005), hundreds of millions of smokers still suffer the consequences of cigarette smoking. Most smokers endorse a desire to quit and 50% do actually quit smoking without any treatment. Of the remaining only about 14–49% achieve abstinence after 6 months of all effective treatments. The pervasiveness of tobacco use, considerable health risks, and far-reaching high societal costs necessitates elucidating the neuroregulatory mechanisms that mediate the acute effects of tobacco smoking as well as the chronic effects of tobacco use.

The dopamine (DA) hypothesis of drug reinforcement including nicotine is supported by a great deal of basic research (see reviews by Di Chiara, 1988, 1999, 2000; Janhunen and Ahtee, 2007). In fact, the evidence that DA is critically involved in nicotine reinforcement led to a treatment, *i.e.*, bupropion. This agent is a phenylethylamine derivative (Dwoskin et al.,

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2006). It has an aromatic aminoketone. Bupropion inhibits DA and, to a lesser extent, norepinephrine transport, resulting in more synaptic DA when it is released. However, overall its effectiveness in treating nicotine dependence is incomplete. One must venture beyond DA to many other possible chemical messengers modulated by nicotine. This review concentrates on endogenous brain opioids and the limited effects produced by nicotine/tobacco smoking.

2. Nicotine/tobacco smoking and brain opioid peptides

The endogenous opioids are part of a large, complex system of neurons in the nervous system, and peripherally via *beta* endorphin release. Some neurotransmitters, such as norepinephrine and serotonin, have cell bodies in defined nuclei that lie in the brainstem and exert widespread influence via axons that project to multiple areas in the brain and spinal cord. The endogenous opioids, however, are produced by neurons scattered throughout the nervous system. Some of these neurons project distantly, and some have a more local influence. In the early 1970s, there was a remarkable increase in basic science investigations of the endogenous opioid system involving multiple receptors and agonist peptides.

Three distinct opioid peptide systems have been identified that are considered members of the endogenous opioid system. Among the final active peptides generated from these precursors are *beta*-endorphin, the met- and leu-enkephalins, and the dynorphins (Waldhoer et al., 2004). Recently, a novel endogenous opioid peptide has been discovered and named nociceptin/orphanin FQ (N/OFQ) (Gustein and Akil, 2006). As with any ligand, the opioids exert their influence by acting on receptors. Three major classes of opioid receptors, *mu*, *delta*, and *kappa*, have been identified using pharmacological methods and cloned (Waldhoer et al., 2004). A fourth member of the opioid peptide receptor family, N/OFQ receptor, was cloned in 1994. In 2000, the Committee on Receptor Nomenclature and Drug Classification of the International Union of Pharmacology adopted MOP, DOP, DOP, and NOP instead of the more widely used terms *mu*, *delta*, *kappa*, and *N/OFQ* opioid receptors. Even now eight years later, most authors prefer the Greek letter designations we have used in this review.

Twenty seven years have elapsed since Karras and Kane (1980) reported that tobacco smoking and craving for tobacco smoke by humans were reduced by the short acting *mu* narcotic antagonist naloxone. This was confirmed, in part, by Gorelick et al. (1988). However, while Nemeth-Coslett et al. (1986) found that mecamylamine affected cigarette smoking, they did not find that it was affected by naloxone. Pretreatment with the *kappa* opioid agonists U50488 and TRK-820 attenuated mecamylamine precipitated withdrawal symptoms in nicotine-dependent rats (Ise et al., 2002). Aceto et al. (1993) reviewed the literature to that date and proposed an opioid role in smoking. Pomerleau's review (1998) further summarized findings of smoking and the role of endogenous opioids to that date. Sutherland et al. (1995) and Wong et al. (1999) used the longer acting narcotic antagonist naltrexone, which also did not alter either human cigarette smoking behavior or its cessation. On the other hand, Krishnan-Sarin et al. (1999) found that naloxone, in a dose-dependent manner, increased opioid like withdrawal signs and symptoms in tobacco dependent smokers compared to nonsmokers. Small doses of naloxone produced increased craving and tiredness in smokers. Those receiving low doses of naloxone also exhibited lower baseline cortisol and attenuated cortisol release in response to naloxone compared to the nonsmokers. Furthermore, King and Meyer (2000) showed that naltrexone significantly reduced desire to smoke, craving and total number of cigarettes smoked, resulting in reduced CO and plasma nicotine levels. Factor analysis of individual differences indicated that smokers with the highest craving during abstinence experienced the greatest naltrexone effect. These investigators concluded that only a subgroup of smokers were sensitive to opioid antagonism.

In animals, nicotine protected against opioid withdrawal (Davenport et al., 1990) and altered brain enkephalins (Houdi et al., 1991). Nicotine self-administration was reduced by high concentrations of the *mu* agonist DAMGO injected into the ventral tegmental area (Corrigall et al., 1999), but not altered by naloxone (Corrigall and Coen, 1991). However, naloxone precipitated a withdrawal syndrome in rats given chronic nicotine, and acute nicotine administration reversed the withdrawal symptoms (Malin et al., 1993; Malin et al., 1996a; Malin et al., 1996b). Nicotine induced DA release in rat nucleus accumbens was prevented by naloxonazine, a *mu* antagonist (Tanda and DiChiara, 1998), but not by naloxone, even though it precipitated a withdrawal syndrome (Carboni et al., 2000). The mixed narcotic agonist-antagonist cyclazocine blocked the DA response to nicotine (Maisonneuve and Glick, 1999). The increase in mesoprefrontal DA utilization and behavioral immobility in chronic nicotine treated animals given acute footshock stress was antagonized by naloxone as was nucleus accumbens DA utilization (George et al., 2000). The documented analgesic effects of nicotine in humans, including plasma *beta* endorphin increases (Pomerleau, 1998; Pomerleau et al., 1983), support a role of nicotine in the release of opioid peptides centrally as well as peripherally. Di Chiara (2000) reviewed additional basic neuroscience data, which further indicate that nicotine caused a significant change in brain opioid peptide mRNA expression.

Pierzchala et al. (1987) showed that repeated short-term administration of small doses of nicotine to male rats produced significant increases in native and peptidase hydroxyable met- and leu- enkephalin in the striatum. These findings are consistent with neuronal release, and with increases in the synthesis and processing of proenkephalin A and prodynorphin-derived peptides. Their findings extend the earlier data of Eiden et al. (1984). Subsequently, Davenport et al. (1990) and Houdi et al. (1991) demonstrated that nicotine caused the release of endogenous opioid peptides. By directly measuring the changes in the steady-state levels of the mRNA for preproenkephalin (PPE) A in rat striatum and hippocampus, Houdi et al. (1998) assessed the changes in enkephalin synthesis rates in response to acute or chronic nicotine administration and its withdrawal. Their data showed that acute treatment with a single injection of nicotine (0.6 mg/kg) elevated PPE mRNA levels in rat striatum and hippocampus, but that chronic treatment (0.6 mg/kg) with nicotine for 14 days produced a decrease in the level of PPE mRNA in these rat brain sites (Houdi et al., 1998). Another important finding of their study is that the withdrawal effect from chronic nicotine produced a rebound increase in the level of PPE mRNA in striatum and hippocampus 24 h following the last treatment with nicotine. These findings have also been observed by others. An increase of PPE mRNA expression in specific brain regions, such as striatum and hippocampus, has also been reported after acute nicotine administration (Dhatt et al., 1995; Isola et al., 2002). Chronic nicotine administration (0.3 mg/kg) lead to an up-regulation of *mu* opioid receptors in the striatum of male and female rats while, at the same time, decreasing striatal met-enkephalin levels (Wewers et al., 1999).

Conclusions

The above review of the literature clearly indicates that nicotine and tobacco smoking modulate the endogenous opioid system in both animals and humans. Despite the impressive amount of published research, it is a fact that opioid antagonists have not been successful in smoking cessation. The few reports of success have not been replicated. Rather than abandon any future studies, it is necessary to better identify the possible psychological and genetic variables that led to study replication failures.

3. Nicotine/tobacco smoking, endogenous opioids and pain

Long ago, humans discovered that opium (and later morphine) is analgesic. In contrast after centuries of use, tobacco (then nicotine) is not useful analgesics in humans. Nevertheless, there are intriguing reports that tobacco/nicotine may modify certain pain perceptions in humans.

Nicotine clearly reduces nociceptive responses in animals. Data on the interaction between tobacco/nicotine/endogenous opioid peptides and their possible role in smoking is mixed, with both positive and negative findings. Hence, many researchers conclude this is a relatively unfruitful area of research. The present is an attempt to provide more “light than darkness” that reveals the complexity of their interaction and a possible guide to future research.

3.1. Human studies

Nicotine/tobacco is not clinically analgesic in humans! Nevertheless, some studies of their use have reported reduced pain. About 170 years ago Somervail (1838) applied tobacco snuff plasters to the skin of patients for local pain relief. Chippendale (1845) applied a tobacco extract ointment over a patient’s neuralgic area. These, presumably local analgesic effects were apparently due to nicotine. Armstrong et al. (1957), Keele (1962), Keele and Armstrong (1964) used exposed sensory nerve endings in the base of a cantharidin blister on the forearm skin of human volunteers. They studied the pain response to locally applied acetylcholine and nicotine. Both substances produced pain. After the initial local stimulant effect of nicotine, the pain response to acetylcholine was abolished. Pomerleau and colleagues have shown that smoking a nicotine-containing cigarette increased the pain awareness thresholds in the cold pressor test (Fertig et al., 1986; Pomerleau et al., 1984). Pauli et al. (1993) demonstrated that cigarette smoking decreased sensitivity to thermal stimuli. Girdler et al. (2005) in their recent study also observed that women smokers had greater threshold and tolerance to ischemic pain than women nonsmokers when pain testing followed rest. Male smokers had greater threshold and tolerance to cold pressor pain than male nonsmokers after both rest and stress. Jamner et al. (1998) further indicated that administration of a nicotine patch decreased pain sensitivity to electrical shock irrespective of smoking status.

It is well known that during withdrawal chronic smokers commonly suffer from dysphoria, discomfort, irritability and other symptoms including pain (First, 1994). Indeed there are some studies reporting increased pain sensitivity during withdrawal, which may be one of the possible factors responsible for the very high smoking relapse rate. Hospitalized patients who were smokers and former smokers, and who had cigarettes and nicotine withheld, used more opiate analgesics than did nonsmokers (Woodside, 2000). Studies using electric shock or exposure to ice-cold water also demonstrated that nicotine-deprived smokers had lower pain thresholds than did smokers supplied cigarettes or snuff (Fertig et al., 1986; Pomerleau et al., 1984; Silverstein, 1982). Kakigi and colleagues (unpublished, 2007) have shown that tobacco smoking did not alter the subject’s perception of laser evoked pain. They found that tobacco smoking did not significantly alter the early evoked potential response (N2) to laser evoked pain, but did significantly reduce the late evoked potential response to laser evoked pain (P2). Nevertheless, the clinical study by Yunus et al. (2002) indicated that fibromyalgia patient smokers complain of significantly more pain than non-smokers.

3.2. Animal studies

There is an extensive literature that acute and chronic nicotine increases thresholds for nociceptive responses in either mice or rats (Aceto et al., 1983; Anderson et al., 2004; Bannon et al., 1998; Caggiula et al., 1995; Carstens et al., 2001; Christensen and Smith, 1990; Craft and Milholland, 1998; Damaj et al., 1993, 1998, 1999; Iwamoto, 1989; Iwamoto, 1991; Khan et al., 1998; Martin et al., 1990; Phan et al., 1973; Rogers and Iwamoto, 1993; Sahley and Berntson, 1979; Tripathi et al., 1982; Yang et al., 1992; Zbuzek and Chin, 1994; Decker et al., 2001, 2004; Vincler, 2005). These basic science antinociceptive studies are interpreted as evidence that nicotine is analgesic. Some pharmaceutical companies have spent millions of research dollars looking for a nicotine analogue which is analgesic with fewer side effects than nicotine with no practical economic success to date.

It is very important to define the type of pain affected by nicotine. Visceral pain induced responses in cats by gall bladder distention with water is reduced by nicotine in doses that do not affect somatic pain (Davis et al., 1932). However, reactions to somatic and especially neuropathic pain may also be reduced by nicotine. For example, Mattila et al. (1965) studied the central and peripheral effects of a series of nornicotine derivatives in mice in comparison to nicotine. Only nicotine and nornicotine transiently increased mouse locomotor activity. Nicotine subsequently decreased their motor activity as a sedative effect. Nicotine and ethylnornicotine prolonged the delay of time in the hot plate test of antinociception. Reserpine pretreatment (which apparently depleted catecholamines) shortened the delay time on the hot plate but did not significantly reduce the analgesic effect of nicotine. The quaternary “ganglionic” nicotinic agonist dimethylphenylpiperazinium (DMPP) did not have similar effects. The fact that mecamylamine blocked the effects of nicotine suggested these were central nervous system effects. Mattila agreed that there may be a correlation between the sedative effects of nicotine and analgesia. The mice were sedated, looked unusual, with rapid respirations after nicotine. Mousa et al. (1988) exposed the rats to smoke from one cigarette (containing 2.65 mg nicotine); they observed that these daily exposure of rats to cigarette smoke induced analgesia after the first exposure day, with the development of tolerance on subsequent days. Other studies indicate that rats receiving chronic infusion of nicotine (6 mg/kg/day) over a 28-day period exhibit analgesia with development of tolerance, in some pain tests (Carstens et al., 2001; Zbuzek and Chin, 1994). Noteworthy is the fact that spontaneous or precipitated withdrawal from chronic nicotine administration (24 mg/kg/day for 14 days) produced hyperalgesia in mice (Damaj et al., 2003). Kishioka et al. (2006) measured serum corticosterone levels in ICR mice as an index of “cross-talk” between nicotine and the opioid system. Single doses of nicotine or morphine elevated corticosterone levels in a dose-effect relationship. The nicotinic antagonist mecamylamine and the opioid antagonist naloxone selectively only antagonized the effects of nicotine and morphine, respectively. Chronic nicotine or morphine was also given twice a day for 7 or 4 days, respectively. Naloxone now increased corticosterone in the chronic nicotine treated mice. Mecamylamine now inhibited the naloxone increase of corticosterone in the chronic morphine treated mice.

Conclusions—Nicotine in relatively large doses is antinociceptive in animals. However, human nicotine/tobacco analgesic studies are unimpressive. Nicotine/tobacco are mild stressors that activate the hypothalamic/pituitary system. The endogenous opioids are important in modulating the endocrine stress response. It is well known that tobacco smoking is increased in humans undergoing stress. Therefore, the endogenous opioid system involvement in this aspect of nicotine/tobacco smoking requires further investigation.

3.3. Direct involvement of the endogenous opioid system in the action of nicotine/tobacco

The hypothesis that nicotine in tobacco smokers may release enough brain opioid peptides to modulate [¹¹C]carfentanil binding has merit (Scott et al., 2007). [¹¹C]Carfentanil is a selective *mu* opioid receptor radiotracer (Titeler et al., 1989) which labels *mu* opioid receptors in both proopiomelanocortin (POMC)/*beta* endorphin pathways (hypothalamus, nucleus accumbens, medial thalamus), as well as in enkephalinergic pathways (striatopallidal pathway). It is sensitive to changes in endogenous opioid activity (Bencherif et al., 2002; Zubieta et al., 2001, 2002, 2003a,b). Therefore, by using positron emission tomography and the radiotracer [¹¹C]carfentanil, labeling *mu* opioid receptor, Scott et al. (2007) in a pilot study examined changes in *mu* opioid receptor mediated neurotransmission from smoking low (denicotinized) to average nicotine content cigarettes. They observed activation of *mu* opioid receptor-mediated neurotransmission (decreased binding potential) from denicotinized to average nicotine conditions only in the right anterior cingulate cortex. In contrast, the *mu* opioid receptor-mediated decreased release (increased binding potential) by nicotine was marked in the amygdala, thalamus, and ventral basal ganglia. These are brain areas implicated in the

anticipation of reward (Kilts, 2001). In addition, they distinguish between potentially rewarding and nonrewarding outcomes (Knutson et al., 2003), affective modulation, and antinociceptive effects (Rainville et al., 1997; Zubieta et al., 2001).

In rodents the administration of the opioid antagonist naloxone decreases nicotine-induced antinociception (Aceto et al., 1993; Campbell et al., 2006; Tripathi et al., 1982; Zarrindast et al., 1997). In addition, nicotine administration prior to the central administration of *beta*-funaltrexamine (β -FNA), an irreversible *mu* opioid receptor antagonist, attenuated β -FNA antagonism of morphine induced antinociception, indicating that nicotine administration led to endogenous opioid peptide release, which activated *mu* opioid receptors and blocked β -FNA's effect (Davenport et al., 1990). The specific involvement of *mu* opioid receptors in this nicotine-opioid interaction has been demonstrated recently, as revealed by the attenuation of nicotine antinociception in *mu* opioid receptor knock-out mice compared to their wild-type counterparts (Berrendero et al., 2002). The findings from this study suggest that nicotine enhances the levels of endogenous opioid peptides derived from preproenkephalin, which would participate in the antinociceptive effects induced by nicotine, presumably by stimulating *mu* opioid receptors. Furthermore, nicotine-induced antinociception in the tail-immersion and hot-plate tests was significantly decreased in preproenkephalin knock-out mice (Berrendero et al., 2005). Tolerance to nicotine-induced antinociception after chronic nicotine administration was accompanied by a decrease of met-enkephalin levels and an upregulation of *mu* opioid receptors in the striatum (Wewers et al., 1999). This suggests compensation of these receptors for the decreased met-enkephalin levels.

The above animal studies indicate that the antinociceptive effects of nicotine involve an endogenous opioid component. Nevertheless, current reviews on nicotinic cholinergic receptor (nAChR) agonists stress that their analgesic effects are quite different from classic narcotic agonists (Decker et al., 2001, 2004; Vincler, 2005). The former have greater involvement of descending noradrenergic and serotonergic neurons (Iwamoto and Marion, 1993).

4. Variables to be considered and controlled in studying nicotine-endogenous opioid interactions

There is a need for scientists to use the basic principles of pharmacology in all of their research designs. Issues of dose, route, time, duration of action, species difference, acute vs chronic administration, tolerance vs withdrawal, tests used, etc. must be adequately controlled.

4.1. Species differences

It is well known that there are marked differences in nicotine actions in different animals and humans. Some mouse strains are stimulated by nicotine in doses that depress in other strains including locomotor activity, seizure, etc. Data obtained in animals must be confirmed in humans if ethically possible.

4.2. Pharmacological Issues

Quantifiable pharmacologic endpoints—If ethically possible, data in animals must be confirmed in humans. For example, the Kishioka et al. (2006) “cross-talk” study described above in mice must be extended to further studies in tobacco smokers. The Krishnan-Sarin et al. (1999) study on serum cortisol in tobacco smokers vs nonsmokers needs replication and extension.

Dose and route of administration—Relevant human tobacco smoking doses should be used in animal studies. This should include evidence that plasma nicotine levels given by any route are relevant to those in humans. Furthermore animal behavioral endpoints should reflect

ongoing normal levels of well being rather than behavioral toxicity. For example, nicotine is clearly antinociceptive in mice, but are such mice behaviorally normal, or do they show some evidence of nicotine toxicity?

Biphasic actions of nicotine-peak and duration of action—Nicotine has long been known to produce stimulant and depressant actions in both humans and animals. The onset, peak and duration of action of each is critical. Nesbit paradox of tobacco smoking (Parrott, 1998) is a good example of the need to clarify these issues.

Acute vs. chronic administration—Tobacco generally is used chronically by humans. Hence the difference in the single acute vs. chronic actions of tobacco/nicotine is critical. Nonsmokers given acute nicotine should be studied far more, if ethically possible, to compare to smokers and former smokers.

Tolerance and behavioral sensitization—Tolerance to many of the effects of nicotine and tobacco are well known. Behavioral sensitization to nicotine is well documented in rodents (Morrison and Stephenson, 1972; Clarke and Kumar, 1983a,b; Ksir et al., 1985, 1987; Hakan and Ksir, 1988, 1991; Johnson, 1995; Johnson et al., 1994, 1995; Domino, 2001). Most neuroscientists assume the same phenomenon occurs in tobacco smokers. Is this true? Obviously much more human research is needed to document this common rat extrapolation.

The times after withdrawal from nicotine/tobacco dependence—These are essential to document. It is a fact that smokers with fibromyalgia complain of more pain than nonsmokers with fibromyalgia patients. Is this because smokers have more pain after short periods of abstinence? Obviously, when tobacco users are studied, the time interval since the last tobacco use becomes very important to document.

Nicotine vs. tobacco smoking—It is frequently assumed that tobacco smoking is primarily due to the reinforcing effects of nicotine. Although there is much data to support this, it is also important to note there is more to tobacco smoking than nicotine alone even in human neuroblastoma cells in culture (Ambrose et al., 2007).

5. Overall conclusions and future directions

Many other neurotransmitters and modulators, apart from endogenous opioid peptides, are involved in the pharmacological effects of nicotine in smokers. A growing body of evidence provides credence to a role of endogenous opioids. It is tempting to consider that regulation of the brain endogenous opioid system by tobacco smoking/nicotine may contribute to continued use, but the evidence to date is weak at best. Withdrawal from nicotine/tobacco not only represents withdrawal from nicotine, but also withdrawal from endogenous opioids and many other neurotransmitters/modulators. Studying the role of the endogenous opioid system at specific times during smoking and its cessation is of value, particularly in that subgroup of smokers who consistently relapse. Finally the endogenous opioid system is involved in regulating many physiological functions both at rest and especially during stress. What is their role in stress and thus modulating the responses to painful stimuli?

Abbreviations

GABA, *gamma*-aminobutyric acid; DA, dopamine; PPE, preproenkephalin; DMPP, dimethylphenylpiperazinium; POMC, proopiomelanocortin; FNA, funaltrexamine.

Acknowledgements

This research was supported in part by NIDA grant DA-01974 and the Education and Research Development Fund 54010.

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