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Interactions between nicotine and morphine in animal paradigms

Interakcje miedzy nikotyną i morfiną w modelach zwierzęcych

Drug addiction is a chronic relapsing brain disease characterized by the compulsive use of addictive substances despite adverse consequences. Polydrug use is becoming increasingly more common, with nicotine and morphine being two of the most commonly co-abused psychoactive drugs. The findings give support for the existence of common pathways in the mechanisms of action of nicotine and opioid receptor agonists, as tobacco smoking increases the craving for opioids. Accordingly, it has been shown that several behavioral and pharmacological actions, including rewarding properties and antinociception, are shared by nicotine and morphine [3–5, 30, 33–34].

MORPHINE- AND NICOTINE-INDUCED ANTINOCICEPTION

Opioid analgesics, such as morphine, are currently the most effective and frequently used pain relievers for moderate to severe pain. However, long-term administration of opioids can alter the central pain-related systems and it results in opioid tolerance (decreased analgesic effect of opioids) and dependence. These effects can significantly hamper the effective treatment of chronic pain with opioid analgesics. On the other hand, nicotine, a major psychoactive constituent of tobacco also has an antinociceptive effect that may afford opportunities for pain relief but may also contribute to the abuse liability of tobacco [3, 4, 27]. Accordingly, cigarette smoking reduces pain in humans and activation of cholinergic pathways by nicotine may also produce antinociception in laboratory animals [6, 34]. It has been revealed that morphine induces antinociception through the activation of the mu-opioid receptors, but also cholinergic mechanisms may be involved in this effect [24]. Moreover, the opioid receptor antagonist naloxone dose-dependently abolished nicotine antinociception and this effect of naloxone was similar to that already described for morphine-induced antinociception [6, 16]. Interestingly, results also showed that antinociception induced not only by morphine but also by nicotine was reduced in morphine-tolerant mice indicating the development of a cross-tolerance between the effects of the two drugs [6, 34]. Chronic morphine administration resulting in the development of tolerance can also induce desensitization (but not a down-regulation) of the mu-opioid receptors [23] and this effect may diminish nicotine-induced acute antinociception in morphine-tolerant mice. The results showing a significant cross-tolerance between nicotine and morphine further emphasize the possibility of common pathways or similar mechanisms involved in the antinociceptive effects of morphine and nicotine. In agreement, the recent study revealed that nicotine-induced antinociception in the tail-flick and hot-plate tests was significantly reduced in the mu-opioid receptor knock-out mice despite the same decrease in locomotion in both wild-type and mutant mice [2].

The close relationship between cholinergic and opioid mechanisms can be discussed in relation to the augmentation of the release and biosynthesis of endogenous opioid peptides in discrete brain nuclei after the activation of nicotinic cholinergic receptors (nAChRs), the main target of nicotine action [15]. Nicotine also protected the mu-receptors from inactivation by the antagonist β-funaltrexamine [10]. In support of this hypothesis, some reports have shown the colocalisation of nAChRs and mu-opioid receptors in several central regions related to supraspinal and spinal control of nociception, such as thalamus and spinal cord [21].

Besides cholinergic and opioid mechanisms, both morphine and nicotine have been reported to stimulate releases of many neurotransmitters [31], such as noradrenaline, serotonin, γ-aminobytyric acid (GABA) or substance P involved in the antinociceptive response of drugs, and this effect may also determine the development of tolerance and cross-tolerance to their antinociceptive responses. Among the neuronal pathways, the recent results show the pivotal role of the serotonergic descending control issuing from the raphe magnus in drug-induced analgesia as a result of the presence of a tonic nicotinic modulation (direct or indirect via GABA/glycine-containing interneurons) of serotonin release [9]. Moreover, spinal noradrenaline release caused by nAChR agonists, either by direct action on adrenergic terminals or indirectly through glutamate release can not be ruled out [18].

MORPHINE AND NICOTINE REWARDING EFFECTS

Besides the acute antinociceptive effects of morphine and nicotine discussed above, some common mechanisms underlying opioid and nicotine dependence have been suggested recently [4,20]. Both morphine and nicotine addiction is a complex behavioral phenomenon dependent on several neurotransmitter pathways, especially on the activation of the mesolimbic dopaminergic system. The clinical data pointed out that some common neurobiological substrates underlie opiate and nicotine dependence and that opioid pathways play a role in mediating smoking behavior, as the opioid antagonist naltrexone is known to reduce the tobacco consumption rate [26].

There is considerable evidence that the rewarding properties of drugs, in human and animals, may be due to their common properties of facilitating (directly or indirectly) dopaminergic transmission, especially in the mesolimbic pathways [12]. Dopamine release within the nucleus accumbens (NAC) is preferentially increased following administration of many drugs commonly abused by humans, including psychostimulants, morphine and nicotine. Although these drugs share in common this ability to increase dopamine turnover in the NAC, their mechanisms of action differ. For instance, morphine stimulation of mu-receptors in the ventral tegmental area (VTA) enhances mesolimbic dopamine transmission presumably by inhibiting GABAergic interneurons and consequently increasing somatodendritic and axonal dopamine release [16]. Nicotine is thought to increase dopamine transmission in the NAC by stimulating the nAChRs located on the dopaminergic neurons in this area [11]. Furthermore, the VTA receives cholinergic projections from the laterodorsal and pedunculopontine tegmental nuclei that directly and indirectly influence the activity of dopamine neurons [22]. In agreement, several studies have demonstrated that the regulation of dopamine release by acetylcholine is needed for rewarding nicotine-induced brain stimulation [32].

Evidence available so far indicates that the negative aspects of nicotine or morphine withdrawal are also regulated by a number of different pathways, and are mediated by different neuroanatomical substrates. It has been documented that spontaneous and antagonist-precipitated nicotine and morphine withdrawal produced marked deficits in dopamine release, especially in the NAC and in the amygdala [14]. In an animal model, it has been shown that morphine reversed withdrawal signs in nicotine-dependent rats [19], while nicotine abolished naloxone-precipitated opioid withdrawal

as well as place aversion induced by naloxone in morphine-dependent rats [1,33]. Additionally, also in the context of physical dependence, experimental studies provided evidence that after chronic administration of nicotine, a single dose of the nicotinic receptor antagonist mecamylamine as well as the opioid receptor antagonist naloxone precipitated somatic withdrawal signs in mice. One can assume that, since nAChR stimulation induces release of opioid peptides, after prolonged nicotine exposure an up-regulation of mu-opioid receptors causes an opioid-like dependence state [30]. Interestingly, previous electrophysiological studies have also reported that the nicotinic receptor may be a target through which opioid compounds might regulate directly nAChR-mediated functions [28]. Thus, it has been shown that nicotine-induced catecholamine secretion was inhibited by naloxone in cultured bovine chromaffin cells resulting from the direct interaction of this opioid antagonist with the nAChR itself [28]. These data further reveal an interaction between cholinergic and opioid receptors in regulating the development of physical dependence.

As stated above, opioidergic/cholinergic interactions may be involved in the control of dopamine release and in the induction of physical dependence, but also in the development of tolerance and sensitization (including crossover effects) induced by nicotine and morphine. Using the conditioned place preference (CPP) test in rats, results also showed cross-reinstatement between morphine and nicotine after short-term extinction. Thus, nicotine place conditioning was reactivated by the single administration of both nicotine and morphine [3, in print]. Recently, in addition to cross-tolerance already stated, data revealed the development of cross-sensitization between nicotine and morphine to their stimulant and rewarding properties [5]. One could argue that drugs can prime responding to one another because they share the property of activating the mesolimbic dopamine system, which becomes sensitized after repeated drug use [7]. The results showed that chronic nicotine treatment sensitized dopaminergic systems to morphine and affected GABAergic systems in the VTA, as in nicotine-pretreated mice morphine-induced dopamine release in the caudate putamen and the NAC was significantly augmented, as measured by microdialysis [17,29]. In the context of dopamine-related behavior, including CPP, it can be noted that nicotine-induced dopamine release in the rat NAC was prevented by mu-opioid receptor antagonist naloxazine [24]. Thus, cholinergic receptors may play a role in this phenomenon, since muscarinic or nicotinic receptor blockade by atropine or mecamylamine, respectively, in distinct brain areas, inhibited morphine-induced CPP in rats [25]. Furthermore, acute morphine administration to rats decreases acetylcholine release in striatum, cortex, and in the core and shell of the NAC [13]. Such an effect is consistent with the common molecular and neurobiological mechanisms shared by nicotine and morphine already discussed, especially in the mesocorticolimbic pathways.

In conclusion, considering that both nicotine and morphine are widely abused, investigating the interactions between nicotine and opioid receptor ligands is of great interest to both basic mechanistic and clinical views. Results of these experiments may contribute to better understanding of neurobiological mechanisms underlying the relapse to nicotine taking and polydrug abuse, and allow developing more effective methods in the treatment of addiction.

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SUMMARY

Nicotine (i.e. tobacco) and morphine are among the most widely consumed drugs in humans. Recent evidence has suggested the existence of common pathways in the mechanisms of action of nicotine and opioid receptor agonists. This paper reviews research of functional interactions between nicotine and morphine in the modulation of behavioral responses in animal paradigms, especially in antinociception and addiction-related processes.

STRESZCZENIE

Morfina i nikotyna są jednymi z najczęściej nadużywanych środków psychoaktywnych u ludzi, wywołujących silne uzależnienie psychofizyczne. Wiele danych literatury wskazuje na istnienie funkcjonalnych interakcji miedzy tymi związkami, co świadczy o współdziałaniu układu opioidowego i cholinergicznego. W pracy zebrano informacje dotyczące tego typu interakcji między nikotyną a morfiną w podstawowych zwierzęcych modelach doświadczalnych, ze szczególnym uwzględnieniem antynocycepcji i działań nagradzających.