been characterized in the locus coeruleus with respect to their complement of nAChR subunit mRNA [3]. To investigate if the nAChR subtypes involved in NA release are affected by chronic nicotine or withdrawal, rats received 0.4 mg/kg nicotine sc once daily for 14 days ± 3 days withdrawal. [^{3}H]NA release in response to 5IA, nicotine and choline was compared in FC and HC prisms in vitro. No differences from saline treated animals were detected in either chronically treated or withdrawn rats in either region examined. This result contrasts with the increase in choline-evoked [^{3}H]NA release in HC prisms following 3 days of withdrawal from nicotine administered via osmotic minipump [1]. This suggests differing responses to sustained and intermittent nicotine administration.

References

[1] Barik W. Mol Pharmacol 2006;69:618–28.
[2] Abin-Carriquiry, et al. Eur J Pharmacol 2006;536:1–11.
[3] Léna, et al. PNAS 1999;96:12126–31.

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3.4

Functional interaction between presynaptic nicotinic and D2 receptors on dopaminergic nerve endings of rat and mouse nucleus accumbens

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It is well known that cross-talk between receptors represent an important mechanism of neurotransmission modulation and plasticity. Although these interactions have been mostly localized postsynaptically, receptor cross-talk which involve common intracellular pathways have been reported to occur also at the presynaptic level [1–3]. Neuronal nicotinic acetylcholine receptors (nAChRs) in the CNS are located mostly presynaptically and have been implicated in facilitating release of neurotransmitters [4]. It has been shown that dopaminergic axon terminals in the nucleus accumbens possess nAChRs mediating enhancement of dopamine (DA) release. We investigated whether nAChRs and DA autoreceptors interact on the same nerve endings using rat and mouse nucleus accumbens (NAc) synaptosomes prelabeled with [^{3}H]DA and exposed to nicotinic and dopaminergic receptor ligands. The nicotinic agonists (-)nicotine or epibatidine provoked [^{3}H]DA release which was inhibited by quinpirole. This effect was blocked by sulpiride and raclopride. The [^{3}H]DA overflow evoked by 4-aminopyridine (4-AP) was markedly inhibited by quinpirole. This inhibitory effect did not change either in absence or in presence of (−)nicotine when the nAChRs were desensitized. The inhibitory effect of quinpirole disappeared after a preincubation with this drug. However, the stimulatory effect of (−)nicotine did not change when the DA autoreceptors were desensitized. (−)Nicotine and 4-AP were able to stimulate [^{3}H]DA overflow also in mouse synaptosomes and this overflow was partially inhibited by quinpirole. In the nAChR subunits β_2 knockout mice the (−)nicotine-evoked [^{3}H]DA overflow was abolished but quinpirole was still able to inhibit the [^{3}H]DA overflow elicited by 4-AP. In conclusion, the (−)nicotine evoked-release can be modulated by D_2/D_3 autoreceptors present on the DA terminals and nAChRs function is independent from the activation of D_2/D_3 autoreceptors which themselves may function independently from the activation of presynaptic nAChRs.

References

[1] Raiteri M, et al. J Pharmacol Exp Ther 1992;260:238–42.
[2] Cheramy A, et al. J Pharmacol Exp Ther 1996;276:616–25.
[3] Pittaluga A, et al. Alcohol Clin Exp Res 2005;313:242–9.
[4] Wonnacott S. Trends Neurosci 1997;20:92–8.

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3.5

Effects of nicotine on real-time dopamine dynamics in rat nucleus accumbens: *In vivo* voltammetric study

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Nicotine, a primary component of tobacco, is one of the most abused drugs worldwide. Success in developing effective treatments for smoking cessation depends on a detailed understanding of the neurochemical changes caused by nicotine in the brain. For many years it has been known that the increase in extracellular dopamine concentration in the nucleus accumbens, a key reward region in the brain, is related to addictive effects of nicotine as well as other drugs of abuse. However, many questions remain unanswered in regard to nicotine-induced changes in the delicate equilibrium between dopamine release and uptake within neurotransmission events that happen on a subsecond timescale. The present study evaluated the effects of nicotine on dopamine release and uptake in the nucleus accumbens of anesthetized rats using fast-scan cyclic voltammetry. The time (ms) and spatial (μm) resolutions of this technique allow a detailed examination of the kinetics of dopamine release and uptake, eliminating the potential contribution of its metabolism. We found that nicotine injection (0.03, 0.1 and 0.3 mg/kg, i.v.) dose-dependently induced dopamine efflux 5–7 s after drug administration. The maximum dopamine concentration was 0.82 ± 0.08 μM. This effect is likely due to nicotine-induced increases in VTA neuron burst firing which has previously been demonstrated in electrophysiological studies. In contrast, nicotine reduced accumbal dopamine release in response to electrical stimulation of the VTA (24 rectangular pulses, 60 Hz, 300 μA, 2 ms/phase). However, no changes in dopamine uptake parameters were detected. The decrease in amplitude of the electrically evoked dopamine signal by nicotine may be due to engagement of dopamine autoreceptors in response to the increased cell firing rate and accumulated extracellular dopamine concentration in the nucleus accumbens. This effect is consistent with observations of nicotine's effect on dopamine in microdialysis studies. Results from this study provide new insight into the acute nicotine-induced changes associated with dopamine release and uptake at the level of presynaptic terminals.

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