The Sensory Impact of Nicotine on Noradrenergic and Dopaminergic Neurons of the Nicotine Reward - Addiction Neurocircuitry

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Abstract

The sensory experience of smoking is a key component of nicotine addiction known to result, in part, from stimulation of nicotinic acetylcholine receptors (nAChRs) at peripheral sensory nerve endings. Such stimulation of nAChRs is followed by activation of neurons at multiple sites in the mesocorticolimbic reward pathways. However, the neurochemical profiles of CNS cells that mediate the peripheral sensory impact of nicotine remain unknown. In the present study in mice, we first used c-Fos immunohistochemistry to identify CNS cells stimulated by nicotine (NIC, 40 µg/kg, IP) and by a peripherally-acting analog of nicotine, nicotine pyrrolidine methiodide (NIC-PM, 30 µg/kg, IP). Sequential double-labelling was then performed to determine whether noradrenergic and dopaminergic neurons of the nicotine reward-addiction circuitry were primary targets of NIC and NIC-PM. Double-labelling of NIC and/or NIC-PM activated c-Fos immunoreactive cells with tyrosine hydroxylase (TH) showed no apparent c-Fos expression by the dopaminergic cells of the ventral tegmental area (VTA). With the exception of sparse numbers of TH immunoreactive D11 cells, dopamine-containing neurons in other areas of the reward-addiction circuitry, namely periaqueductal gray, and dorsal raphe, were also devoid of c-Fos immunoreactivity. Noradrenergic neurons of locus coeruleus (LC), known to innervate VTA, were activated by both NIC and NIC-PM. These results demonstrate that noradrenergic neurons of LC are among the first structures that are stimulated by single acute IP injection of NIC and NIC-PM. Dopaminergic neurons of VTA and other CNS sites, did not respond to acute IP administration of NIC or NIC-PM by induction of c-Fos.

Figure 1: Fluorescent and laser scanning confocal microscopy images of representative brainstem sections demonstrating nicotine (NIC) and nicotine pyrrolidine methiodide (NIC-PM) activation of noradrenergic neurons of locus coeruleus (LC). Panels A-C: Control data demonstrating the effects of acute intraperitoneal injection of physiological saline (PS) on c-Fos activation of tyrosine hydroxylase (TH)-immunoreactive (IR) cells of LC. Panels D-I: Low power fluorescent (D-F) and high power confocal (G-I) images showing NIC-induced c-Fos IR cells (D, G), TH IR cells (E, H) and merge images of c-Fos with TH IR cells in LC. Panels J-L: High power confocal images showing NIC-PM induced c-Fos IR cells (J), TH-IR cells (K) and merge images of c-Fos with TH-IR cells (L) in LC. Arrows point to representative double-labeled neurons.

Semi-quantification

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In the most caudal extent of VTA (bregma -3.87 mm to -3.51 mm), NIC and NIC-PM activated c-Fos IR cells were sparsely scattered among the dopaminergic cells of paranigral nucleus (PN), parainterfascicular nucleus (PIF) and parabrachial pigmented nucleus (PBP). c-Fos IR cells were also detected at sites medial and ventral to the dopaminergic cells in regions which correspond to interpeduncular nucleus rostral (IPR) and pontine nuclei (Pn). More rostrally in the anterior extension of VTA (bregma -3.15 mm to -3.07 mm), NIC and NIC-PM activated cells were found mainly ventral and medial to the dopaminergic cells of VTA rostral (VTAR) and PBP, at sites which overlapped interfascicular nucleus (IF), rostral linear nucleus (RLi), IPR and retromamillary nucleus (RM) (Figure 3).

c-Fos IR cells were also seen medial and dorsal to the dopaminergic

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