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SELECTIVE DOWN-REGULATION OF [^{125}I]Y_0-α-CONOTOXIN MII BINDING IN RAT MESOSTRIATAL DOPAMINE PATHWAY FOLLOWING CONTINUOUS INFUSION OF NICOTINE

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Abstract—Prolonged exposure to nicotine, as occurs in smokers, results in up-regulation of all the neuronal nicotinic acetylcholine receptor subtypes studied so far, the only differences residing in the extent and time course of the up-regulation. α6β2*-Nicotinic acetylcholine receptors are selectively enriched in the mesostriatal dopaminergic system and may play a crucial role in nicotine dependence. Here we show that chronic nicotine treatment (3 mg/kg/day for two weeks, via s.c. osmotic minipumps) caused a significant decrease (36% on average) in the binding of [^{125}I]Y_0-α-conotoxin MII (a selective ligand for α6β2*-nicotinic acetylcholine receptors in this system) to all the five regions of the rat dopaminergic pathway analyzed in this study. After one week of withdrawal, binding was still lower than control in striatal terminal regions (namely the caudate putamen and the accumbens shell and core). In somatodendritic regions (the ventral tegmental area and the substantia nigra) the decrease was significant at the end of the treatment and recovered within one day of withdrawal.

This effect was not due to displacement of [^{125}I]Y_0-α-conotoxin MII binding by residual nicotine. In fact the binding was not changed by 565 ng/g nicotine (obtained with a single injection of nicotine), a concentration much higher than that found in the brain of rats chronically treated with nicotine (240 ng/g). In addition, consistent with previous studies reporting an up-regulation of other subtypes of nicotinic acetylcholine receptors, we found that nicotine exposure significantly increased (40% on average) the binding of [^{125}I]epibatidine (a non-selective agonist at most neuronal heteromeric nicotinic acetylcholine receptors) in three up to five regions containing only α-conotoxin MII-insensitive [^{125}I]epibatidine binding sites, namely the primary motor, somatosensory and auditory cortices. In conclusion, this work is the first to demonstrate that α6β2*-nicotinic acetylcholine receptors, unique within the nicotinic acetylcholine receptor family, are down-regulated following chronic nicotine treatment in rat dopaminergic mesostriatal pathway, a finding that may shed new light in the complex mechanisms of nicotine dependence.
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Key words: α-conotoxin MII, chronic treatment, withdrawal, up-regulation, nicotine.

Up to now, 11 nicotinic acetylcholine receptor (nAChR) subunits have been cloned in mammalian nervous system (the α2-α7, α9, α10 and β2-β4 subunits), which can assemble to form a variety of ligand-gated pentameric ion channels (Itier and Bertrand, 2001). Three major subtypes of neuronal nAChRs have been described: the α4β2*-nAChRs and the α7-nAChRs, which are expressed predominantly in the CNS and the α3β4*-nAChRs, abundant in the peripheral nervous system. These receptors present different pharmacological characteristics, desensitization kinetics and nicotine-induced up-regulation (Quick and Lester, 2002; Gentry and Lukas, 2002).

More recently, a new subtype of neuronal nAChRs is attracting the attention of the scientific community: the α6β2*-nAChRs. These receptors are distributed in the neurons of the dopaminergic mesostriatal pathway and in few other brain structures (Champtiaux et al., 2002). The aim of this work was to determine if also α6β2*-nAChRs undergo persisting changes after chronic nicotine exposure and during nicotine withdrawal. To pursue this objective, rats were treated chronically with nicotine, according to a protocol previously shown to produce up-regulation of other nAChR subtypes (Mugnaini et al., 2002). Surprisingly, we found a decrease in the binding density of [^{125}I]Y_0-α-conotoxin MII (α-CtxMII), a radioligand which binds with high affinity to native α6β2*-nAChRs (Champtiaux et al., 2002). These data suggest that the α6β2* is the first nAChR subtype for which a nicotine-induced down-regulation has been demonstrated.

A preliminary report of this work has been presented at the 4th Forum of European Neuroscience Societies (Mugnaini et al., 2004).

EXPERIMENTAL PROCEDURES

Adult male Wistar rats (Charles River, Italy), weighing 250–300 g, were used in all experiments. The research complied with Italian national legislation, with the company policy on the Care of Use of Animals and with related codes of practice. Every attempt was made to minimize the number of animals required and to minimize their suffering. Rats were individually housed with free access to water in a temperature-controlled environment on a 12-h light/dark cycle, and maintained under restricted diet regimen (18–22 g/day) to keep their weight stable throughout the duration of the experi-

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Abbreviations: AcbC, core of nucleus accumbens; AcbSh, shell of nucleus accumbens; Au1, primary auditory cortex; B-H, Benjamini-Hochberg's; CPu, caudate putamen; α-CtxMII, α-conotoxin MII; MT, medial terminal nucleus of the accessory optic tract; M1, primary motor cortex; nAChR, nicotinic acetylcholine receptor; ox, optic chiasm; SNPC, pars compacta of substantia nigra; S1, primary somatosensory cortex; VTA, ventral tegmental area; Zo&SuG, zonal and superficial gray layer of superior colliculus.

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ment. Nicotine dose was expressed as mg of free base/kg of body weight.

Rats received a single s.c. administration of either saline or nicotine (0.6 mg/kg) and were killed by decapitation 30 min after the injection. Alternatively, rats were implanted s.c., under isoflurane anesthesia, with Alzet Osmotic Minipumps (model 2-ML2) with a pumping rate of 5 μl/h delivering saline or nicotine. Five groups of six rats each were infused s.c. for 14 consecutive days with saline (six rats) or with 3 mg/kg/day of nicotine (24 rats). Saline-treated rats and a group of six nicotine-treated rats were

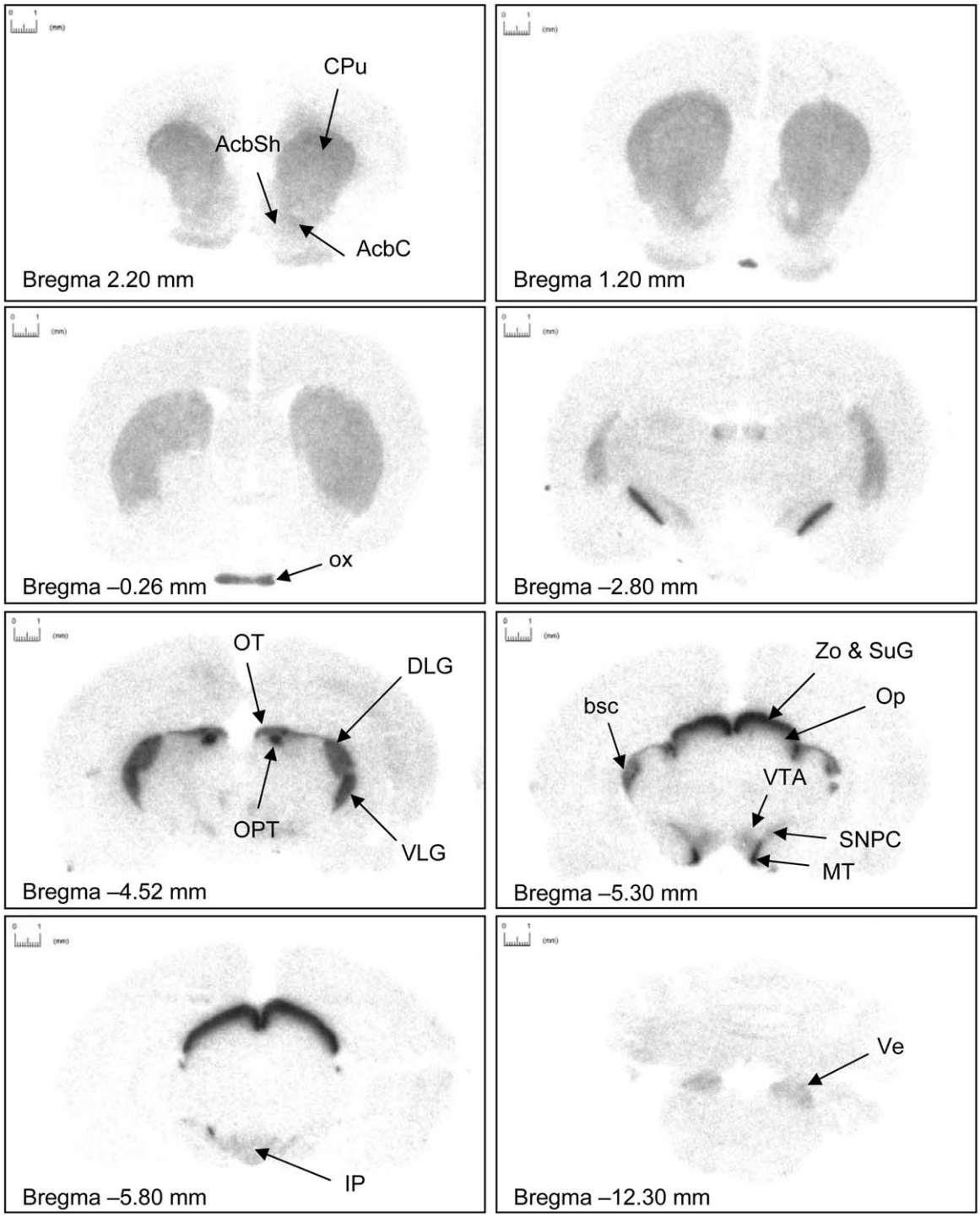

Fig. 1. Distribution of [^{125}I]Y_0-α-CtxMII binding sites in rat brain. Coronal brain sections were incubated in 0.5 nM radioligand for 2 h at room temperature, as described in Experimental Procedures. The rostrocaudal level of each section was defined as distance from the Bregma in stereotaxic coordinates (shown in figure; Paxinos and Watson, 1998). Scale bars=1 mm. bsc, brachium of superior colliculus; DLG, dorsal lateral geniculate; IP, interpeduncular nuclei; Op, optic layer of superior colliculus; OPT, olivary pretectal nucleus; OT, nucleus of optic tract; Ve, vestibular nuclei; VLG, ventral lateral geniculate.

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