

COVER ESSAY

Patterns of nicotine action in the brain

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Through the efforts of dedicated scientists over many decades, it has been established that nicotine is a drug that enters the brain, where it binds to specific receptors and alters brain function. This information, critical to the realisation that nicotine is the active ingredient in tobacco that leads to addiction, derives in part from important technical advances which include radiotracer assays for receptor binding and regional brain metabolism.

Receptor-binding assays provide information about the initial sites of drug action. Nicotine has its primary action at the nicotinic cholinergic receptor, an ion channel that allows intracellular entry of sodium ions when activated by the endogenous neurotransmitter acetylcholine or by agonists such as nicotine. *In vitro* assays using radiolabelled nicotine were combined with autoradiographic studies to demonstrate the anatomical localisation of specific binding sites for the drug in the rodent brain.¹ The sites show high concentrations in components of the limbic system, such as the medial habenula and the interpeduncular nucleus, thalamic nuclei, components of the visual system, and the cerebral cortex. It is noteworthy that the ventral tegmental area, a midbrain region identified as important to the rewarding properties of drugs of abuse, has a substantial concentration of these sites. The wide distribution of specific binding sites for nicotine in the brain demonstrates the potential impact of nicotine administration on behaviour. Subsequent studies using autoradiography in mice that were given injections of radiolabelled nicotine substantiated the fact that systemically administered nicotine rapidly reaches the same sites in the brain that are labelled with the drug *in vitro*.²

Because of the distributed network systems in the brain, however, drugs can produce effects at regions of the brain that are remote from initial receptor interactions. Metabolic mapping with radiolabelled deoxyglucose provides an assessment of rates of glucose utilisation throughout the central nervous system. Glucose is the major metabolic substrate of the adult brain for oxidative metabolism, and transient perturbations in brain function also stimulate non-oxidative use of glucose. Therefore, assays of glucose utilisation provide a useful index of local brain function. The deoxyglucose approach can identify brain areas that are affected directly or indirectly, through afferents, by exogenous administration of a psychoactive drug, such as nicotine.

The demonstration of specific binding sites for nicotine *per se* was not a demonstration that these sites were coupled to functional change.

For this purpose, and also to visualise the distribution of the functional response to nicotine in the brain of an intact organism, studies using deoxyglucose were performed in rats.^{3,4} The animals showed dose-dependent stimulation of cerebral glucose utilisation, with marked increases in those areas of the brain that were shown to have high densities of specific binding sites for nicotine. The photographs on the cover of this issue of *Tobacco Control* illustrate this stimulation in brain sections from rats that were given nicotine (shown on the right), as compared with sections from matching planes of brain from rats that received no drug (left). Brain regions showing stimulation included the thalamus (top), components of the habenulo-interpeduncular system (second pair of images), parts of the visual system (third pair), and the cerebellum (bottom). These studies demonstrated the impact of nicotine on various systems in the brain, including those involved in sensory and motor activities, and autonomic function, as well as limbic systems involved in motivation. Subsequent studies using the deoxyglucose method in rats have shown tolerance to the actions of nicotine in discrete areas of the brain.⁵

Because of the advent of noninvasive imaging techniques, the future for this line of investigation includes human studies. The deoxyglucose method as well as radiotracer methods for rapid assessments of cerebral blood flow, another cerebral functional index, can be extended to pharmacological investigations in human volunteers by the use of positron emission tomography (PET) scanning.⁶ PET studies can be paired with simultaneous measures of mood and feeling state. The use of PET offers the promise to identify neuroanatomical substrates of the mood-altering properties of nicotine as well as the brain regions important to the performance deficits associated with nicotine withdrawal.

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- 3 Broussolle EP, DF Wong, RJ Fanelli, ED London. *In vivo* specific binding of [³H]-nicotine in the mouse brain. *Life Sci* 1989; 44: 1123-32.
- 4 London ED. Effects of nicotine on cerebral metabolism. In: G Bock, J Marsh, eds, *The biology of nicotine dependence*. Ciba Foundation Symp No 152. Chichester: Wiley, 1990; 131-46.
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