The Effect of Chronic Nicotine and Withdrawal on Intra-Axonal Transport of Acetylcholine and Related Enzymes in Sciatic Nerve of the Rat


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With 3 Figures

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Summary

The content of acetylcholine (ACh) and activities of the cholinergic enzymes choline acetyltransferase (CAT) and ACh-esterase (AChE) were studied in intact and crushed rat sciatic nerve after chronic nicotine administration and withdrawal 2 days before the final experiment. Nicotine was given in the drinking water during 8—10 weeks and the final dose reached was about 8 mg/kg/day, i.e. equivalent to that of the heavy cigarette smoker.

In the chronic nicotine group, ACh levels and AChE activity of uncrushed nerve were significantly decreased as compared to the controls. The accumulation of ACh and AChE proximal to a single crush was also somewhat decreased, but significant only for AChE at 18 hours postoperatively. After withdrawal of nicotine for 2 days the ACh content of both uncrushed and 12 hours crushed nerves were further decreased, while AChE was instead increased to control (uncrushed) or even supranormal (18-hour crush) levels.

Key words: Cholinergic substances, chronic nicotine, withdrawal, oral administration, rat sciatic, intra-axonal transport.

Introduction

Chronical treatment of rats with nicotine in low doses increases the turnover of noradrenaline (NA) in the brain (Bhagat, 1970). Acute i.v. administration can also cause a release of acetylcholine...
(ACh) from cat brain cortex (Armitage et al., 1969), and of 3H-NA from hypothalamus in cat (Hall and Turner, 1972). In vitro nicotine releases ACh from rat cerebral synaptic vesicles (Chiou et al., 1970). In the cat hindleg, nicotine intra-arterially has a stimulating or depressing action on the neuromuscular junction, depending on the dose given (cf. Paton and Savini, 1968; Volle and Koelle, 1970). Thus, there are several observations that indicate that the peripheral motor neuron may be influenced by nicotine in a number of ways; (a) an increased turnover of NA in nerve terminals of bulbo-spinal NA neurons, ending close to the motor somata in the gray matter of the spinal cord (Dahlström and Fuxe, 1965), may influence the motor neuron, (b) a release of ACh from vesicles or end-plates may occur also in the peripheral motor neuron, and (c) nicotine influences transmission at the motor end-plate. Intra-neuronal events in the motor neuron may be influenced by these nicotine effects indirectly, but the drug could also have direct effects on the neuron. Nicotine may affect the motor neuron, e.g. by altering intra-axonal transport of substances directly involved in transmission.

In a previous study (Heiwall et al., 1976) we have demonstrated that acute administration of low doses (30 μg/kg s.c.) of nicotine may influence the intra-axonal transport of mainly the transmitter-metabolizing enzyme acetylcholine esterase (AChE) in rat sciatic nerves. The present study was undertaken to study the effect of chronic nicotine administration and withdrawal on the intra-axonal transport of acetylcholine (ACh), AChE and choline-acetyltransferase (CAT) in rat motor nerves. The dose of nicotine given was chosen to mimic the serum concentrations of nicotine in a heavy tobacco smoker.

**Material and Methods**

**Nicotine Treatment**

About 100 male Sprague-Dawley rats (130 g initial weight) were used and divided into 3 groups. Two groups received nicotine in the drinking water (tap water) during 8—10 weeks. This administration route was successfully used by Wenzel and Azmeh (1970). The nicotine concentration was low initially (5×10⁻⁸ mg/ml) and was increased gradually to 0.1 mg/ml (see Fig. 1). The third group (controls) were given plain water. All rats were kept 5 in each cage, and housed together at 25 °C on a constant 12-hour lighting schedule. The water intake per cage and the body weight of all groups of animals were registered at regular intervals. The nicotine solutions, prepared from nicotine base (Leo or Merck) were studied regularly by spectrofluorimetric assays of Millipore-filtered samples to control the stability of the nicotine. This varied between different batches of nicotine.