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Research Report

# Intraperitoneal injection of pilocarpine activates neurons in the circumventricular organs and hypothalamus in rats

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ABSTRACT

It has been suggested that while the sialogogue pilocarpine elicits salivary secretion by acting directly on acinar cells of the salivary glands, it induces drinking behavior by acting on muscarinic receptors in the central nervous system. To study which brain regions are affected by the peripherally injected pilocarpine, we investigated changes in the numbers of c-Fos immunoreactive cells. The injections increased the numbers of c-Fos immunoreactive cells in the subfornical organ, median nucleus of preoptic area, organum vasculosum of lamina terminalis, paraventricular nucleus and supraoptic nucleus. Intracerebroventricular injection of pilocarpine produced similar changes in the expression of c-Fos immunoreactivity. The increases in immunoreactive expression induced by both the intraperitoneally and intracerebroventricularly injected pilocarpine were suppressed by previous intracerebroventricular injection of the muscarinic receptor antagonist atropine. Electrophysiological experiments using slice preparations and whole cell recordings showed that pilocarpine depolarized the membrane of neurons in the subfornical organ and suppressed the inhibitory GABAergic synaptic currents by a presynaptic action. The results suggest that peripherally applied pilocarpine does not act only on the salivary glands as a sialogogue, but also evokes thirst sensation by acting on the center controlling body fluid balance in the central nervous system.

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## 1. Introduction

Pilocarpine, a muscarinic receptor agonist, is a typical sialogogue used to treat hyposalivation (Gotrick et al., 2004). We have found that while pilocarpine administered peripherally affected the salivary glands via the blood vessels and made the oral cavity wet by increasing saliva (Gotrick et al., 2004; Omori et al., 2003), it facilitated drinking behavior (Fregly, 1980; Sato et al., 2006). The behavior was suppressed by the intracerebroventricular (ICV) injection of the muscarinic receptor antagonist.

The subfornical organ (SFO) and organum vasculosum of lamina terminalis (OVLT) in the circumventricular organs lack the blood-brain barrier (BBB) and are strongly involved in drinking behavior (Fitzsimons, 1998; Johnson and Gross, 1993). We have recently reported the existence of muscarinic receptors in the SFO and have found that activation of the receptors produces excitatory responses (Honda et al., 2003; Ono et al., 2003; Xu et al., 2001). Therefore, we hypothesized that peripherally administered pilocarpine might affect neurons in such circumventricular regions directly. Further, since the SFO and OVLT

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send efferent projections to the median nucleus of the preoptic area (MnPO), and the paraventricular (PVN) and supraoptic (SON) nuclei in the hypothalamus, which are also related to drinking behavior and body fluid balance, pilocarpine may also affect neurons in the hypothalamic nuclei.

To investigate this hypothesis, the expression of c-Fos immunoreactivity (IR), which was used as a marker for neural excitation, was examined in the SFO, OVLT, MnPO, PVN and SON. In addition, we investigated the c-Fos IR in the nucleus of tractus solitarius (NTS) which is a relay nucleus of visceral afferent information. Further, rat brain slice preparations and patch clamp recording techniques were used to look at whether pilocarpine influenced neural activity in the SFO.

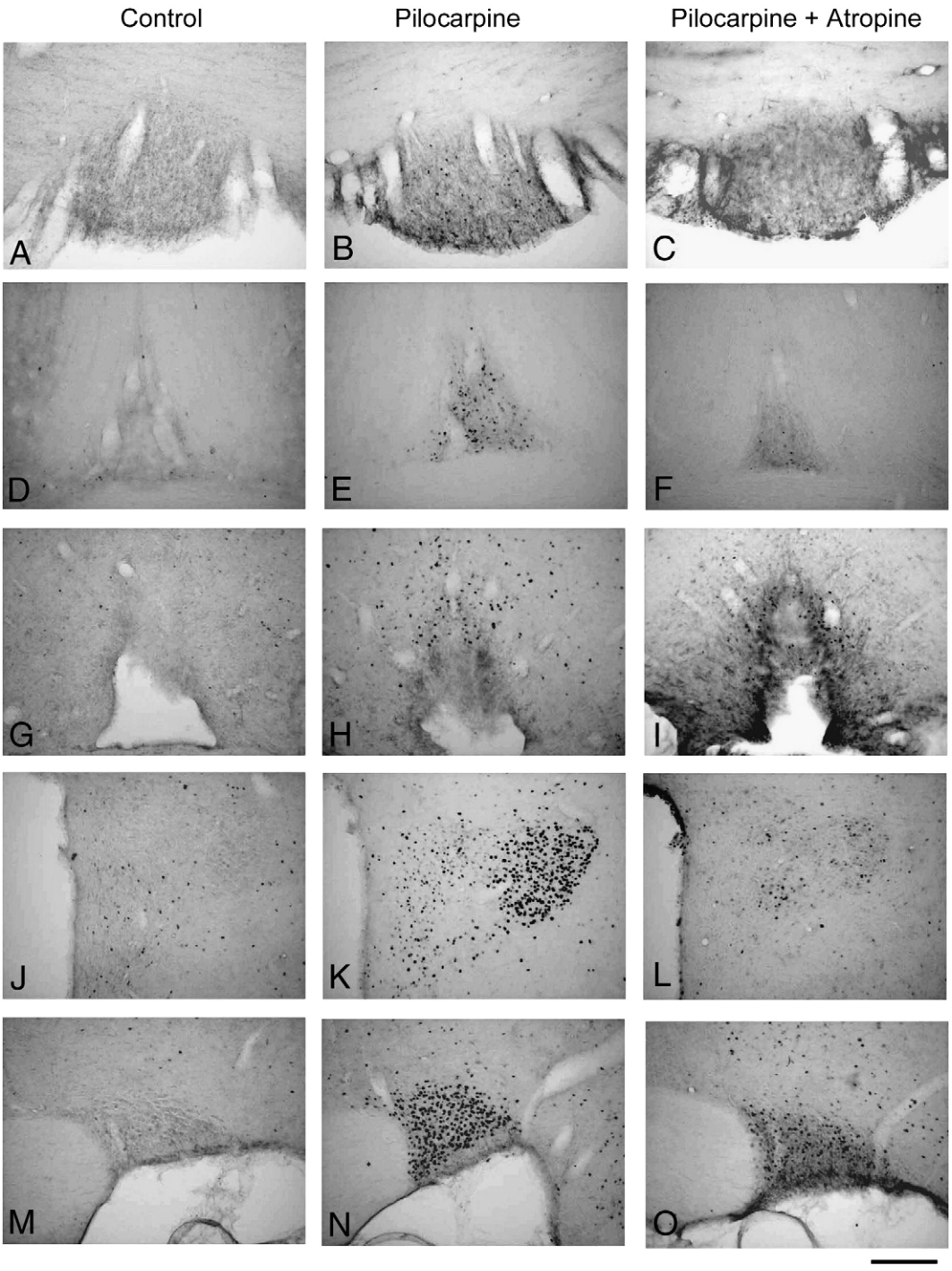


**Fig. 1 – The increased c-Fos IR in the forebrain regions produced by intraperitoneally injected pilocarpine and its suppression with the prior ICV injection of atropine. c-Fos IR was tested in the SFO (A–C), MnPO (D–F), OVLT (G–I), PVN (J–L) and SON (M–O). Panels in the left, center and right columns show the results in the control, after the IP injection of pilocarpine (12 μmol/mL/kg) and after the co-injection of pilocarpine and atropine, respectively. Atropine (1 nmol, 6 μL ) was intracerebroventricularly injected 5 min before the pilocarpine injection. A bar in O indicates 200 μm.**

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