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Research Report

Damage of the medial preoptic area impairs peripheral pilocarpine-induced salivary secretion

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ABSTRACT

The existence of neural connections between the medial preoptic area (MPOA) and the salivary glands and the increase in salivation by thermal or electrical stimulation of the MPOA have suggested an important role of MPOA in the control of salivary gland function. Although direct cholinergic activation of the salivary glands induces salivation, recent studies have suggested that salivation produced by i.p. pilocarpine may also depend on the activation of central mechanisms. Therefore, in the present study, we investigated the effects of bilateral electrolytic lesions of the MPOA on the salivation induced by i.p. pilocarpine. Adult male Holtzman rats (n = 11–12/group) with bilateral sham or electrolytic lesions of the MPOA were used. One, five, and fifteen days after the brain surgery, under ketamine anesthesia, the salivation was induced by i.p. pilocarpine (1 mg/kg of body weight), and saliva was collected using preweighted small cotton balls inserted into the animal's mouth. Pilocarpine-induced salivation was reduced 1 and 5 days after MPOA lesion (341 ± 41 and 310 ± 35 mg/7 min, respectively, vs. sham lesions: 428 ± 32 and 495 ± 36 mg/7 min, respectively), but it was fully recovered at the 15th day post-lesion (561 ± 49 vs. sham lesion: 618 ± 27 mg/7 min). Lesions of the MPOA did not affect baseline non-stimulated salivary secretion. The results confirm the importance of MPOA in the control of salivation and suggest that its integrity is necessary for the full sialogogue effect of pilocarpine. However, alternative mechanisms probably involving other central nuclei can replace MPOA function in chronically lesioned rats allowing the complete recovery of the effects of pilocarpine.

1. Introduction

Salivary secretion is controlled by both sympathetic and parasympathetic systems. Parasympathetic stimulation activating muscarinic cholinergic receptors in the salivary glands induces salivary gland vasodilatation and salivation (Emmelin, 1987; Garret, 1987; Garret et al., 1991). Increases in salivary secretion also result from peripheral administration of cholinergic agonists like pilocarpine or methacholine (Emmelin, 1987; Ferguson, 1993; Garret, 1987; Moreira et al., 2001, 2002; Renzi et al., 1993, 2002; Takakura et al., 2001; Wiseman and Faulds, 1995).

In addition to the well-known peripheral mechanisms mediating cholinergic-induced salivation, there is also

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evidence suggesting the involvement of central mechanisms in the sialogogue effect of pilocarpine. The evidence for the central mechanisms is based on studies showing that (1) lesions of the anterior preoptic–periventricular tissue surrounding the third ventricle (AV3V region) or of the lateral hypothalamus (LH) reduce pilocarpine-induced salivation (Renzi et al., 1993, 2002); (2) the blockade of encephalic cholinergic muscarinic receptors by intracerebroventricular injections of atropine methyl bromide in a low dose that acts only centrally reduces by 75% the salivation induced by systemic pilocarpine (Takakura et al., 2003); (3) peripheral pilocarpine-induced salivation is strongly reduced by activation of central alpha$_2$-adrenoceptors (Moreira et al., 2001, 2002; Takakura et al., 2001).

The reduction of pilocarpine-induced salivation by focused central lesions is a consistent effect that, however, lasts less than 2 weeks (Renzi et al., 1993, 2002). Although the animals remain refractory to ingestive behavior dependent on homeostatic challenges, the recovery of several basic vital functions like daily food and water intake occurs after severe impairment produced by damage of structures like AV3V and LH (Gonçalves et al., 1992). In the case of pilocarpine-induced salivation, it seems that neural plasticity is such that it overcomes the removing of these brain areas, but it is also possible that lesions so far produced were not in more critical areas that mediate pilocarpine-induced salivation. A critical area perhaps involves structures that project directly to the salivary glands and thereby are essential for salivary secretion. The medial preoptic area (MPOA) is a candidate to be such critical area. Anatomical data suggest direct projections from the MPOA to the parasympathetic preganglionic neurons that control the salivary glands (Hübschle et al., 1998), and salivary secretion from the submandibular/sublingual complex is facilitated by thermal or electrical stimulation of the MPOA (Kanosue et al., 1990). The AV3V lesions that strongly reduce pilocarpine-induced salivation also partially destroy MPOA (Renzi et al., 1993). Therefore, MPOA damage may play a role on the reduction of pilocarpine-induced salivation by AV3V lesions.

In spite of the evidence showing the involvement of the MPOA in the control of salivary gland function, no previous study investigated the possible participation of the MPOA in the cholinergic-induced salivation. Therefore, in the present work, we investigated the effect of electrolytic lesions of the MPOA on the salivation induced by peripheral pilocarpine.

2. Results

2.1. Histological analysis

Fig. 1 shows typical bilateral lesions of the MPOA in a slice of a rat brain representative of the lesioned rats. The MPOA lesions (n = 33) were placed from 0.5 to 1 mm lateral to the third ventricle and had approximately a circular shape with 0.3 to 0.4 mm of radius. The lesions were restricted to the MPOA and left intact all the periventricular tissue, the anterior medial preoptic nucleus, and the anteroventral preoptic nucleus (Paxinos and Watson, 1986). Misplaced lesions were located in the septohypothalamic nucleus (n = 5), anteroventral preoptic nucleus (n = 5), or unilateral MPOA lesion (n = 5). Since the results of these misplaced lesions were similar, they were grouped together.

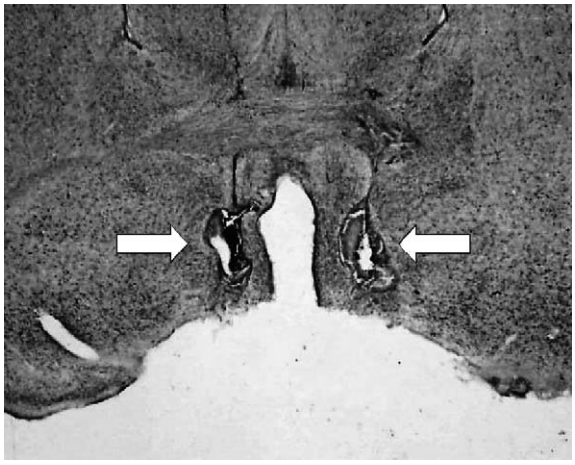

Fig. 1 – Photomicrography showing the bilateral MPO lesions (arrows).

2.2. Pilocarpine-induced salivation in MPOA-lesioned rats

In MPOA-lesioned rats (24 h and 5 days), the salivation induced by i.p. pilocarpine (1 mg/kg of body weight) was reduced by 22% [$F(1,42) = 2.1$, $P < 0.05$] and by 38% [$F(1,40) = 14.7$, $P < 0.001$] compared to the respective sham lesion groups (Figs. 2A and B). However, pilocarpine-induced salivation was not different from controls at 15 days after MPOA lesions (Fig. 2C).

The MPOA lesions did not alter the baseline salivation (Fig. 2).

2.3. Pilocarpine-induced salivation in rats with lesions outside the MPOA

Misplaced lesions did not alter pilocarpine-induced salivation (Table 1).

3. Discussion

The results show that i.p. pilocarpine-induced salivation was reduced acutely (from 24 h to 5 days) after bilateral electrolytic lesions of the MPOA in rats, but salivation was completely recovered chronically, at 15 days after the lesion surgery. Although MPOA lesions reduced pilocarpine-induced salivation, they did not affect non-stimulated baseline salivary secretion.

The involvement of forebrain areas in the control of salivary secretion has been demonstrated by several studies (Flynn et al., 1981; Hainsworth and Epstein, 1966; Kanosue et al., 1990; Matsuo and Kusano, 1984; Renzi et al., 1993, 2002; Schallert et al., 1978; Whyte and Johnson, 2002, 2005). Thermoregulation-induced salivary secretion in the