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REVIEW (JAOB/Rising Members Award)

Neural Mechanisms of Swallowing Inhibition Following Noxious Orofacial Stimulation

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Abstract : The number of water-induced swallows was decreased following capsaicin injection into the facial (whisker pad) skin, masseter or lingual muscle. The capsaicin-induced inhibitory effect on the swallowing reflex was depressed after intrathecal administration of mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor. The inhibitory effect on swallowing following capsaicin injection into the lingual muscle was diminished by paratrigeminal nucleus (Pa5) lesioning. Many phosphorylated extracellular signal-regulated kinase-like immunoreactive neurons in the nucleus tractus solitarii (NTS) showed gamma-aminobutyric acid (GABA) immunoreactivity and capsaicin-induced inhibition of the swallowing reflex was diminished by local microinjection of the $GABA_A$ receptor antagonist into the NTS.

The present findings suggest that facial skin-NTS, masseter muscle-NTS, lingual muscle-NTS and lingual muscle-Pa5-NTS pathways are involved in the swallowing inhibition by facial, masseter and lingual pain, and that the activation of GABAergic NTS neurons may be involved in inhibition of the swallowing reflex.

Introduction

Swallowing is considered an essential movement for life because of two vital functions, alimentation and protection of the upper respiratory tract[1)]. Swallowing has commonly been subdivided into oral, pharyngeal and esophageal phases[1—3)]. The oral phase is considered as a transport event which moves the food bolus from the oral cavity to the oropharynx ; the pharyngeal phase is understood a reflex movement composed of pharyngeal peristalsis, closure of the glottis and relaxation of the upper esophageal sphincter ; and the esophageal phase is accepted as the primary peristalsis of the esophagus controlled by somatic and autonomic nervous systems[1—4)]. It is also generally accepted that the swallowing central pattern generator in the medulla can be activated by inputs from the cerebral cortex based on previous clinical observation, and electrophysiological and neuroimaging studies[5—8)].

Capsaicin is known as a specific irritant to activate C-fibers and small diameter Aδ-fibers via transient receptor potential V1 in the fiber terminals[9)]. There have been a number of reports using capsaicin treatment of the peripheral nerve fibers to clarify the pain perception mechanisms[10,11)]. In this study, capsaicin

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was used as the specific irritant to activate noxious fibers.

It has been shown that electrical stimulation of the trigeminal nerve or high-intensity orofacial stimulation resulted in strong inhibition of jaw-closing motor neurons, regarded as a nocifensive reflex[12,13]. Furthermore, electrical stimulation of the lingual nerve inhibited the swallowing reflex[14,15]. It has also been reported that inflammatory myopathy or abnormal persistent oral pain following dental extraction are involved in swallowing difficulties[16,17]. These studies support the idea that trigeminal nociceptive inputs may be involved in the modulation of swallowing. Therefore, it is important to evaluate trigeminal nociceptive effects on the swallowing reflex in order to elucidate the neural mechanisms of dysphagic patients caused by abnormal orofacial pain.

Effect of Capsaicin on Swallowing

Some previous reports suggested that a small amount of capsaicin treatment of the oral and pharyngeal mucosa improves the swallowing reflex by releasing substance P in the plexus pharyngeus[18,19]. Ebihara *et al*. demonstrated that the latency of the swallowing reflex (LTSR) in elderly people treated with a capsaicin troche was significantly shorter than in the control group[19]. In addition, LTSR in the intervention group became significantly shorter after treatment compared to before treatment. Furthermore, improvement of the swallowing reflex as a result of daily capsaicin application was prominent in the high-risk group, whose LTSR was longer than 6.0 seconds. These data suggest that capsaicin treatment of the oral and pharyngeal mucosa is a useful possible treatment for oropharyngeal dysphagic patients.

We measured the number of swallowings induced by distilled water (DW) administration into the pharyngolaryngeal region following capsaicin injection into the whisker pad skin, masseter and lingual muscle. Although many previous studies used electrical stimulation of the superior laryngeal nerve or glossopharyngeal nerve for initiation of swallowing, our methodological advantage is to observe naturally induced swallowing by water administration[1,20—22]. The number of swallows was significantly decreased following high concentration capsaicin (10 and 30 mM) injection into the whisker pad skin, masseter or lingual muscle compared to the vehicle (Fig. 1). These data suggest that orofacial nociceptive inputs are strongly involved in inhibition of the swallowing reflex.

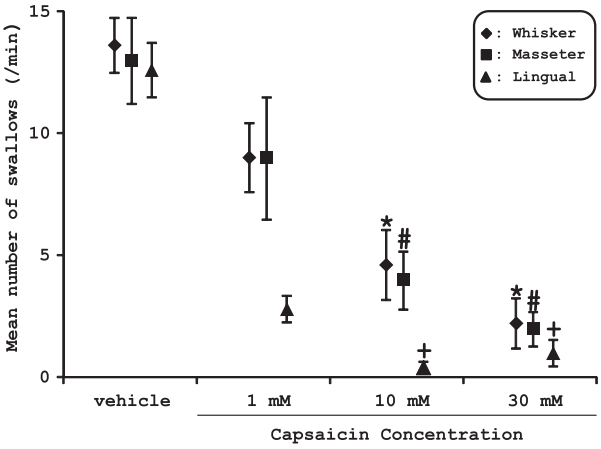

Fig. 1 The number of DW-induced swallows following different concentrations of capsaicin injection into whisker pad skin, masseter or lingual muscle

$*p<0.05$ compared to vehicle injection into whisker pad skin, $\#p<0.05$ compared to vehicle injection into masseter muscle, $+p<0.05$ compared to vehicle injection into lingual muscle. Results are presented as the mean ± SEM.

Involvement of ERK Phosphorylation in Swallowing Inhibition

Because the pERK is thought to be a reliable marker of neurons activated by various noxious stimuli, we counted the number of pERK-like immunoreactive (LI) neurons in the brainstem following 10 mM capsaicin injection[23]. The number of pERK-LI neurons in the NTS and trigeminal spinal subnucleus caudalis (Vc) following capsaicin injection into the whisker pad skin, masseter or lingual muscle was significantly larger than with vehicle administration. The number of pERK-LI neurons in the paratrigeminal nucleus (Pa5) following capsaicin injection into the lingual muscle was also significantly larger than with vehicle treatment.