Amitriptyline increases salivary flow in treatment-resistant burning mouth syndrome: What is the underlying mechanism?

Burning mouth syndrome (BMS) is characterized by intolerable pain in the mouth with no underlying dental or medical causes, and sometimes accompanied with complaints of xerostomia. BMS patients showed lower salivary flow and higher salivary spinnability. Salivary flow rates in BMS patients are decreased further by amitriptyline, which is widely used as an analgesic for BMS. However, we found that amitriptyline increased salivary flow in treatment resistant BMS patients. We compared salivary flow between amitriptyline-responders and non-responders. The salivary flow before treatment was actually low in non-responders. Furthermore, non-responders indicated a statistically significant increase in salivary flow with amitriptyline, while responders showed a significant decrease (Fig. 1).

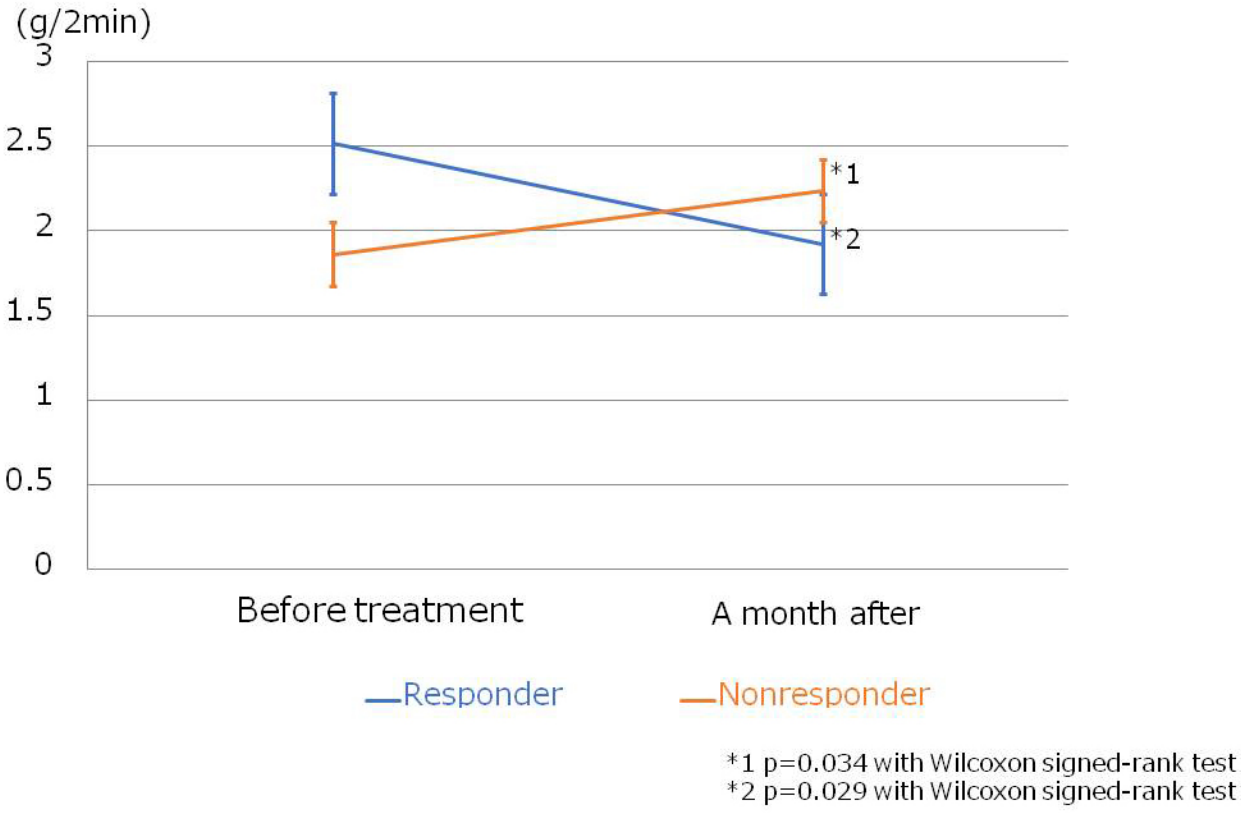

Fig. 1. The changes in salivary flow with amitriptyline in responders and non-responders.

Principal control of salivary secretion is derived from two types of neurotransmitters released by

autonomic nerves: acetylcholine (Ach) and noradrenaline (NA). Ach evokes a copious flow of saliva via increased parasympathetic tone, and NA produces a viscous flow via increased sympathetic tone. Amitriptyline caused a dose-related decrease in salivary flow by blocking Ach, while it increased protein-rich salivary flow by increasing NA. When parasympathetic tone reduces, amitriptyline may increase salivary flow by enhancing NA. Non-responders may cause a decline in parasympathetic tone because of low salivary secretion before treatment. According to the increased salivary flow, non-responders can be expected an increased sympathetic tone with amitriptyline. Central noradrenergic neurons are traditionally viewed as pain inhibitory. However, complex interactions among brainstem pathways and their receptors modulate both inhibition and facilitation of pain. Chronic pain induces brainstem noradrenergic activation that enhances descending facilitation from the dorsal reticular nucleus (DRt). This suggests that antidepressants inhibiting noradrenaline reuptake may enhance pain facilitation from the brainstem, counteracting their analgesic effects at the spinal trigeminal nucleus caudalis in treatment resistant BMS patients. In non-responders, an increase in NA by amitriptyline may not only enhance pain facilitation from the brainstem but also increase a viscous salivary flow (Fig. 2).

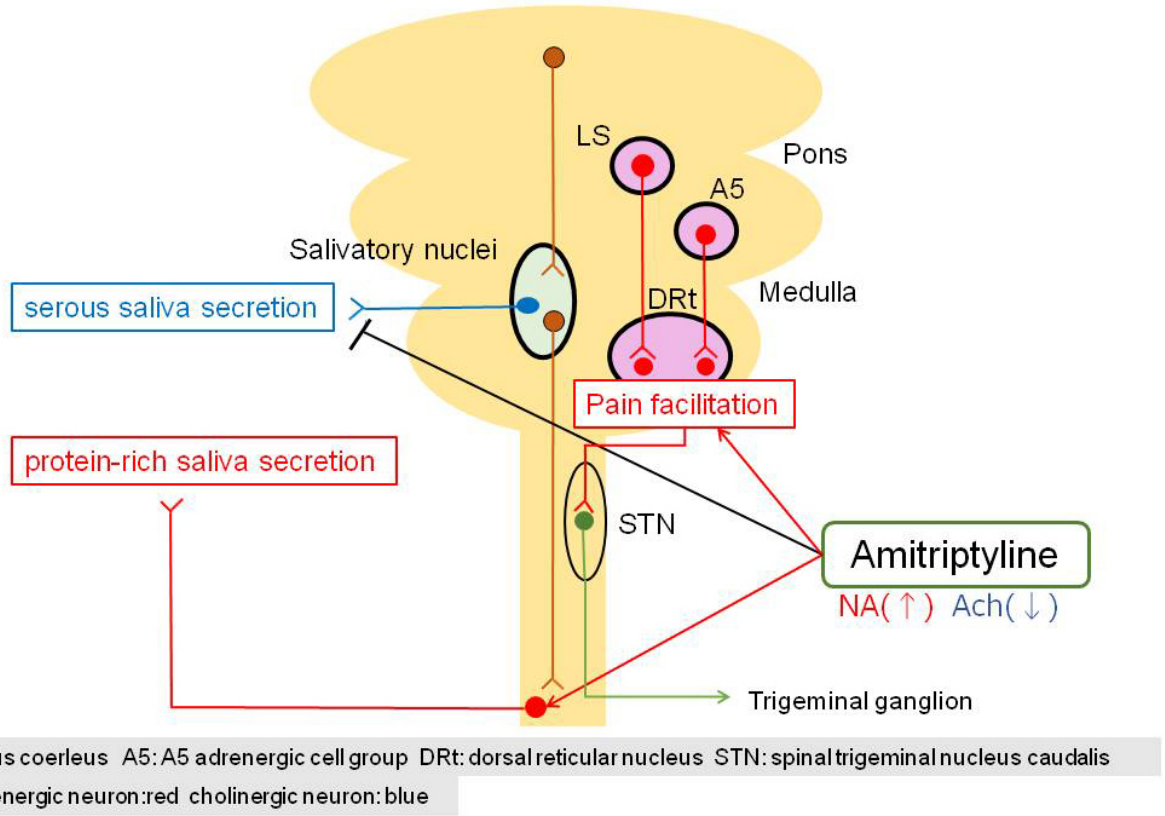

Fig. 2. The effect of amitriptyline on salivary secretion and the descending pain facilitation system in non-responders.

Amitriptyline has been a first-line treatment for BMS for many years. The fact that there is no supportive unbiased evidence for a beneficial effect of amitriptyline is disappointing, but has to be balanced against decades of successful treatment in many BMS patients. Amitriptyline should continue to be used as part of the treatment of BMS, but only a minority of people will achieve satisfactory pain relief. We eager to know a marker for analgesic effects of amitriptyline on BMS. The changes in salivary flow of BMS patients may be a reliable and non-invasive estimation of clinical response to amitriptyline.

Takeshi Watanabe [1], ***Kaoru Kawasaki*** [1], ***Trang T.H Tu*** [1], ***Akira Toyofuku*** [1], ***Takahiko Nagamine*** [2]

[1]*Department of Psychosomatic Dentistry, Tokyo Medical and Dental University, Japan,*
[2]*Sunlight Brain Research Center, Japan*

Publication

An increase in salivary flow with amitriptyline may indicate treatment resistance in burning mouth syndrome.
Kawasaki K, Nagamine T, Watanabe T, Suga T, Tu TTH, Sugawara S, Mikuzuki L, Miura A, Shinohara Y, Yoshikawa T, Takenoshita M, Toyofuku A
Asia Pac Psychiatry. 2018 Mar 25