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Intranasal Oxytocin and NSAIDs

Kenneth K Kwong^{*,†} and Suk-tak Chan^{*}

^{*}MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

It is with great interest that we read the article “Oxytocin nasal spray in fibromyalgic patients” published in *Rheumatology International*. Mameli et al. [1] reported negative therapeutic effects from intranasal oxytocin self-administered by 14 women with fibromyalgia.

The negative outcome was intriguing as literature suggested an inverse relationship between endogenous plasma oxytocin levels [2] and severity of fibromyalgia pain and symptoms. Menstrual cycle-related change in plasma oxytocin [3] might also be related to the swing of fibromyalgia symptoms [4].

We hypothesize that the lack of analgesic or therapeutic efficacy of intranasal oxytocin might be related to the concomitant use of anti-inflammatory pain killers. Self-medication with nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted both before and during the fibromyalgia study [1]. Twelve out of fourteen patients registered the use of NSAIDs during the study.

In a presentation at the 2013 International Headache Congress, Yeomans et al. [5] reported that chronic migraine patients, taking NSAIDs such as ibuprofen within 24 hours prior to receiving intranasal oxytocin, experienced significantly less relief compared with patients not taking NSAIDs. Yeomans et al. raised two concepts: 1) Expression of oxytocin receptors is driven by inflammatory cytokines. 2) The anti-inflammatory properties of NSAIDs block the oxytocin receptors in the trigeminal system.

Without the interference of NSAIDs, intranasal oxytocin reduced pain in 42% of chronic migraine patients at 2 hrs and 55% at 4 hrs, compared to 11% and 28% for placebo. Migraine is one of the major symptoms of fibromyalgia. So Yeomans’ presentation [5] has significant relevance to fibromyalgia research.

Yeomans et al. focused on the trigeminal pathway of intranasal oxytocin to reach the brain. The trigeminal results did not discount the existence of other possible pathways such as the olfactory bulb [1, 6].

[†]**Corresponding author:** Athinoula A. Martinos Center for Biomedical Imaging, Building 149, Thirteenth Street, Mail Code 149-2301, Charlestown, MA 02129, USA. Phone: (617) 724 9519. Fax: (617) 726 7422. kwong@nmr.mgh.harvard.edu.

Conflict of interest None.

In an answer to a comment by Rash et al. [7] of their paper, the authors Agabio, Mameli et al. [8] cited a review [9] of the scarcity of clinical human studies on the analgesic effect of oxytocin. Five out of the seven studies used oxytocin nasal spray [1, 10–13], relevant to our comment. Out of the five, only one paper [10] reported, in comparison with placebo, some positive effect of intranasal oxytocin on *chronic pain*. It recorded a negative effect on chronic constipation, the main target of the study, but reported a weak positive effect on abdominal discomfort.

The citations by Agabio, Mameli et al. [8] did miss a 2013 Chinese study [14] which showed a successful dose dependent analgesic effect of intranasal oxytocin spray for headache treatment.

It is interesting to speculate that less access to NSAIDs, similar to the case in [5], may contribute to the positive outcome of the two cited oxytocin reports on chronic pain [10, 14]. In the abdominal discomfort case [10], NSAIDs are not the treatment of choice for chronic constipation. In the Chinese headache study [14], the subjects were asked not to take any analgesic medication during the experiment and the patients did not receive any treatments before the experiment. Unfortunately, no explicit records of the exclusion of NSAIDs were given in [10, 14]. Future intranasal oxytocin studies should take NSAIDs into consideration.

The results of the chronic constipation study may offer a suggestion to the role of intranasal oxytocin. Intranasal oxytocin, presumably acting on the brain through neuronal pathways [5], may block the abdominal pain signals of the guts from reaching the brain. But intranasal oxytocin may not fare better than placebo on constipation [10] if intranasal oxytocin has only a weak interaction with oxytocin receptors at the GI tract [10, 15] through plasma oxytocin [16].

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