

# Congress Proceedings

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## **Oxytocin - A Possible Mediator of Anti Stress Effects Induced by Acupuncture?**

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Oxytocin, a polypeptide containing nine amino acids, is produced in the paraventricular and the supraoptical nuclei of the hypothalamus. Oxytocin is secreted into the circulation to produce hormonal effects such as stimulation of milk ejection and uterine contractions. In addition, oxytocin is released from oxytocin containing nerve fibres that reach various areas in the brain, such as other parts of the hypothalamus, the amygdala, the raphe nuclei, the PAG, the striatum and the brainstem centres for control of autonomic function. Thus oxytocin may influence endocrine functions, but also exert anxiolytic and sedative effects, elevate pain threshold, decrease sympathetic nerve activity and increase vagal parasympathetic nerve activity. Taken together oxytocin induces a psycho-physiological pattern consistent with increased social behaviour, anti-stress and promotion of growth. These effects become particularly prominent if oxytocin is given repeatedly. Five daily injections of oxytocin elevate pain threshold for 10 days after the last injection and blood pressure may be reduced for up to three weeks in female rats. When the anti-stress is established it can be maintained by treatment given at longer intervals.

The long-term effects of oxytocin and some of the acute effects are mediated by secondary changes in the activity in other transmitter systems. The pain relieving effects involve an increased activity in central opioid systems e.g. in the PAG, whereas the anti-stress effects are mediated by an enhanced activity in the  $\alpha 2$  adrenoceptors in various brain areas reached by oxytocin containing nerves. Since these receptors exert an inhibitory effect on noradrenaline (NA) release, the activity in the central NA bundles emanating from the locus coeruleus, which is linked to arousal and aggression, is decreased. At the same time activation of EPI neurons in the brainstem lead to an inhibition of the peripheral sympathetic system, and an increase in the activity of the parasympathetic system, and as a consequence anti-stress and growth promotion is induced.

Originally it was assumed that oxytocin was only released during labour and breastfeeding in response to activation of sensory nerves in the mammary gland and uterus. However, it has recently been established that oxytocin can be released in response to touch, warmth and light pressure from all parts of the body. Obviously stimulation of non-noxious somatosensory afferents does not only result in 'a localised sensation of touch', it also results in physical relaxation and a sense of well-being. In a rat model, in which the abdomen is being stroked with a frequency of 40 strokes per minute for 5 minutes, all the effects that can be induced by oxytocin (increased friendly social interaction and the anti-stress effects) are induced. Administration of an oxytocin antagonist inhibits the effects of the massage-like stroking acutely, but also the long-term effects seen after repeated treatments. Interestingly, the massage-like stroking induces more powerful effects if applied on the ventral surface. This can be an effect that is secondary to the denser innervation of this region. However, immunohistological studies have revealed the presence of an extra type of sensory nerve originating in the skin on the ventral surface. These do not project to the spinal cord, but directly to the vagal nerve to reach the NTS. Thus some of the cutaneous afferents travel to the brain via the afferents from the viscera e.g. the gastrointestinal tract. The NTS is in turn directly connected to the PVN where oxytocin is produced. It is possible that activation of these special cutaneous afferents lie behind the more powerful effects of touch, warmth and light pressure,

when triggered from the ventral surface.

The mechanisms by which acupuncture induces its effects are only partly known and are under debate. However, particularly the long-term anti-stress effects of this treatment may well include activation of oxytocinergic pathways and mechanisms. Some animal experimental data indicate that pain relief induced by acupuncture is abolished not only by opioid antagonists but also by oxytocin antagonists. Oxytocin has also been shown to alleviate back and cancer induced pain in humans. Further studies are needed to explore the relationship between oxytocin and the effects of acupuncture.

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### **Acupuncture Mechanisms and the Relevance to Clinical Practice**

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Acupuncture is part of traditional Chinese medicine, a system with an empirical basis that has been used in the treatment of pain for centuries. Its use for pain relief is supported by clinical trials and this has facilitated its acceptance in pain clinics in most countries. Acupuncture effects on pain must devolve from physiological and/or psychological mechanisms with biological foundations. Acupuncture and some other forms of sensory stimulation elicit similar effects in man and other mammals, suggesting that they bring about fundamental physiological changes. Acupuncture excites receptors or nerve fibres in the stimulated tissue which are also physiologically activated by strong muscle contractions and the effects on certain organ functions are similar to those obtained by protracted exercise. Both exercise and acupuncture produce rhythmic discharges in nerve fibres, and cause the release of endogenous neurotransmitters including opioids, monoamines, oxytocin and other neuropeptides (SP, CGRP, GAL, CRF, NPY), important in the control of both sensory, affective and cognitive elements of pain.

Over the past ten years there has been a growing awareness that pain is due not simply to the activation of peripheral nociceptors, as in nociceptive pain, but to multiple factors, and is therefore susceptible to various modes of acupuncture treatments. Depending on the aetiology, pain may be classified into several categories, such as nociceptive, neurogenic, chronic pain syndrome and psychogenic pain.

Musculoskeletal and visceral pain states, both nociceptive, are characterised by hyperalgesia. However, despite belonging to a similar category, the pain is triggered by different mechanisms. Neurogenic pain is caused by injury or dysfunction in the nervous system and is often severe and intractable and may not respond to even powerful opioids. Recent studies suggest that there is a third pain category, distinct from the neurogenic and nociceptive, where pain is related to a sickness response that occurs with exposure to chemical compounds and infectious agents the associated central changes produce heightened pain sensitivity ('hurting all over'), termed chronic pain syndrome. In clinical trials acupuncture or low frequency electroacupuncture have shown to be effective in some nociceptive pain states, whereas high frequency stimulation is more effective in neurogenic pain. In chronic pain syndrome patients with high anxiety, acupuncture is generally inefficient. It is possible that part of the lack of effect in chronic pain syndromes can be attributed to high levels of the opioid-antagonist cholecystokinin in the brain.

Acupuncture may be effective in some categories of pain but the mode of stimulation should be adjusted to the aetiology of pain. Also, patients are likely to respond better if they are not stressed and anxious.

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