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Nociceptive behavior induced by mustard oil injection into the temporomandibular joint is blocked by a peripheral non-opioid analgesic and a central opioid analgesic.

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Abstract

The aim of this study was to improve the mustard oil (MO) induced temporomandibular joint (TMJ) nociception model and to investigate the potential analgesic activity of systemic dipyrone and tramadol on the nociceptive behavioral responses induced by injection of low concentrations of the MO into the rat TMJ region. TMJ injection of 2.5% MO produced a significant nociceptive behavior expressed by head flinching and orofacial rubbing. This activity was related to the MO injection since mineral oil (vehicle) did not elicit response. Local application of the lidocaine N-ethyl bromide quaternary salt, QX-314 (2%) and systemic administration of morphine (4 mg/kg) significantly reduced the MO-induced nociceptive responses, validating the nociceptive character of the behaviors. The pretreatment with systemic dipyrone (19, 57 or 95 mg/kg) as well as tramadol (5, 7.5 or 10 mg/kg) was effective in decreasing the nociceptive behavioral responses induced by the injection of MO into the rat TMJ. In conclusion, TMJ injection of low concentrations of MO in rats produces well defined and quantifiable nociceptive behaviors constituting a reliable behavioral model for studying TMJ pain mechanisms and testing analgesic drugs. The results also suggest that dipyrone and tramadol could be effective analgesic options in the management of TMJ pain.

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hyperalgesia. Often the term hyperalgesia is used for both hyperalgesia and allodynia. For example, the paw withdrawal to a thermal stimulus after inflammation (see Figure 1) is thermal allodynia because withdrawal occurs at a normally innocuous temperature (38.5°C), yet it is typically described as thermal hyperalgesia (Hargreaves and others 1988). Nevertheless, a distinction can be made between these two types of behaviors in animals and the underlying mechanisms investigated.

As shown in Figure 3A, the injection of CFA into the rat's hind paw reduced the yon Frey threshold from 8.5 to 1.2 g. This result suggests that innocuous mechanical stimuli that are ordinarily barely perceptible now produce a paw withdrawal response. However, is this hyperalgesia or allodynia? The use of response duration as a measure (Figure 3B) suggests that this is mechanical allodynia. After CFA, rather than rapidly returning the stimulated paws to the test surface, the rats hold it off the floor for longer durations, sometimes shake it, and sometimes lick it. More intense mechanical stimuli that normally result in an increase in response duration result in additional increases, suggesting the presence of mechanical hyperalgesia (Figure 3B).

Intradermal capsaicin produces a model of neurogenic inflammation and hyperalgesia (LaMotte and others 1991) similar to one utilized in human subjects. The intradermal injection of capsaicin results in primary hyperalgesia at the site of injection and a surrounding area of secondary hyperalgesia to light touch. A flare reaction extends into the zone of secondary hyperalgesia. This neurogenic inflammation model has been used in monkeys to study changes in nociceptor activity and changes in the responses of spinal dorsal horn neurons (LaMotte and others 1991; Simone and others 1991). The model has recently been adapted to behavioral studies in the rat (Gilchrist and others 1996). Withdrawal responses to heat and mechanical stimuli were assessed using the paw withdrawal latency method described above (Hargreaves and others 1988; Ren and Dubner 1993). Intraplantar injection of capsaicin evokes nocifensive behavior characterized by lifting and guarding of the injected paw that lasts about 3 min. Capsaicin produces changes in paw withdrawal latencies and their duration to heat and mechanical stimuli in a dose-dependent manner. Reduced withdrawal latencies to heat last up to 45 min, whereas the effects of mechanical stimuli persist up to 4 h.

Other inflammatory agents such as mustard oil, a small fiber irritant, and zymosan have been used to produce behavioral and physiological changes. The effects of mustard oil are relatively short (a few minutes) when applied topically to cutaneous tissues (Ma and Woolf 1996a; Neumann and others 1996). Mustard oil can also be given by injecting subcutaneously or into muscle, in which case the changes last up to 20 min (see below) (Yu and others 1994). The intraplantar injection of zymosan produces a persistent dose- and time-dependent thermal and mechanical hyperalgesia associated with an intense inflammation (Meller and Gebhart 1997). A comparison of the onset and duration of inflammatory hyperalgesia produced by these inflammatory agents appears in Table 1.

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Table 1
Comparison of inflammatory models of pain and hyperalgesia

Orofacial Inflammation.

The formalin test is also applicable to the study of orofacial pain mechanisms. Clavelou and others (1989) gave injections of formalin into the upper lip of the rat. They observed that the rat's initial reaction to the

formalin injection involved immediate head movement often accompanied by vocalization. After 15 to 30 sec, rats start to rub vigorously the injection site with forelimbs or hindlimbs; the duration of rubbing appears to correlate well with the pain intensity. The first phase of the perioral formalin test lasts only about 1 min, which is shorter than that seen in the paw formalin test. The timing of the second phase of the formalin test is similar after perioral or paw injections. This method has been shown to be a reliable method for assessing pain in the trigeminal region.

Mustard oil is also used to produce acute orofacial inflammation. After injection of mustard oil into the temporomandibular joint of the rat, inflammation develops within 30 min and reaches maximum in 2 hr (Haas and others 1992). The electromyographic (EMG[1]) activity is significantly increased in digastric and masseter muscles after mustard oil injection into the temporomandibular region (Hu and others 1994). The increase in EMG activity lasts for several minutes, which suggests the involvement of a central sensitization process. Because the effects of mustard oil last a relatively short time, this model has not been used to assess behavioral hyperalgesia and allodynia in the orofacial region.

To produce more persistent orofacial inflammation, CFA is given by injection into the orofacial region (Ren and Dubner 1996). The orofacial inflammation produced by CFA lasts more than 1 wk as indicated by plasma extravasation in the injected site (Zhou and others 1997). Interestingly, the same amount of the inflammatory agent produces significantly more intense inflammation after injection into the temporomandibular joint versus perioral skin. The behavioral hyperalgesia and allodynia have been evaluated after CFA-induced orofacial inflammation. By employing the method described above, it was found that thermal hyperalgesia developed at 5 hr, peaked at 24 hr, and lasted at least 1 wk after CFA injection into the temporomandibular joint or perioral skin (Ren and Dubner 1996). This time course of hyperalgesia is very comparable with that seen in the hind paw inflammation models (Hargreaves and others 1988; Hylden and others 1989). The mechanical sensitivity of the facial skin at the perioral injection site also was significantly increased, suggesting the development of mechanical allodynia.

Hyperalgesia and Allodynia.

Behavioral models of hyperalgesia and allodynia have been useful in the study of peripheral and central mechanisms of hyperalgesia and allodynia. They have been correlated with neural events in primary afferent neurons and CNS neurons, particularly at the level of the medullary and spinal dorsal horns. Although correlative electrophysiological and behavioral studies have been informative (LaMotte and others 1991; Ren and Dubner 1993; Ren and others 1992; Simone and others 1991; Woolf and Thompson 1991; Yu and others 1993), only a few neurons can be studied. Recently, Fos, the protein product of the c-fos immediate early gene, has been used as a measure of neuronal activity (Bullitt 1990; Hunt and others 1987). Fos protein is induced by neuronal activity and appears to play a role in long-term changes in the CNS after neural activity (Goelet and others 1986). Fos expression increases in many nociceptive neurons in the dorsal horn after inflammation, and these changes can be localized to specific populations of neurons using immunocytochemical methods. The findings can be correlated with behavioral hyperalgesia and allodynia after injection of inflammatory agents such as CFA, carrageenan, mustard oil, or formalin (Draisci and Iadarola 1989; Gogas and others 1991; Ma and Woolf 1996b; Mentrey and others 1989; Presley and others 1990; Ren and Ruda 1996; Wei and others 1998, 1999).

Joint Inflammation

Acute arthritis can also be induced by the injection of carrageenan and