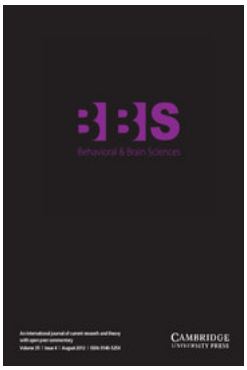

Pains, brains, and opium

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One interpretation the authors offer is that there may be estrous variations in colonic visceral pain, with pain being greatest in proestrus. However, other interpretations are possible. Another relevant finding in these two studies was that colonic pressures induced by distension did not vary with estrous stage. What this result means is that, during proestrus, smaller fecal boli would trigger defecation.

Proestrus is the reproductive stage in which rats are fertile and most easily aroused by hindquarter tactile stimulation. Thus, it may be that the rat's similarly more sensitive visceromotor and colonic responses to colonic distension during proestrus promote emptying of the colon to facilitate successful fertilization during copulation. Whether there would be an accompanying change in colonic pain is unclear, but seems unlikely. Supporting this interpretation is the finding that cardiovascular responses showed no estrous increases during proestrus. Thus, the clinical relevance of these findings might be more applicable to gastrointestinal motility issues (Wald et al. 1981) than to colonic pain. But, of course, as discussed above in section R9.3, all of these conclusions might change under conditions of colonic pathophysiology (Giamberardino et al. 1997).

R9.5. Sex hormones. It is often a knee-jerk response to assume that any sex or estrous/menstrual stage variations in an entity are due to sex hormones. As discussed in section R9.3 above, this assumption is clearly unwarranted until further study has demonstrated it. Although the issue of sex hormones and pain is an important one, few, if any, human studies have focused on it.

Finally, however, a recent study has directed its full attention on the impact of hormones on a pathophysiological pain condition in humans. In an elegant and well-controlled epidemiological study based on automated pharmacy records of women enrolled in a large health maintenance organization in the northwestern United States, LeResche and colleagues (1997) found that the odds of having temporomandibular disorder pain were increased by approximately 20% and 30%, respectively, in young women who used oral hormone contraceptives and postmenopausal women who used estrogen (or estrogen and progestin) replacement therapies. For the postmenopausal women, these odds increased with increased doses of estrogen. No clearcut increased risk was observed with progestin use.

Although an immediate conclusion from these findings might be that women and their doctors should add an increased risk of temporomandibular pain to their list of cons when weighing the pros and cons of oral contraceptive or estrogen replacement therapy, the authors themselves are rightly very cautious and self-critical in their assessment of the implications of their findings. They make no statements on the clinical applicability of their findings. However, they rightly point out the provocativeness of their findings and provide a long list of future studies to test how generalizable their findings are to other populations and other painful disorders. If their findings do prove generalizable, then understanding the mechanisms that give rise to this increased risk will certainly have a powerful clinical impact.

In sum, these previous five sections not only provide convincing arguments that sex is one of the potent factors underlying pain, they also indicate that progress is well underway toward a better understanding of how to apply the information clinically.

R10. Conclusions [Kupers, Binik, Rollman, and Gijsbers & Niven]

Are sex differences relevant to mechanisms of persistent pain and its treatment? **Kupers,** via Molière, provides a clear answer: "oui et non." I here provide a less clear one: "yes."

Gijsbers & Niven remind us that our conclusions should be based "not on the insignificance of sex differences in behaviour and perception but on their complexity," and that only through further study will we "come to understand the extent to which individual differences in suffering are dependent on generalisable sex differences." **Rollman** states that when it comes to caring for a single human of either sex, we "need to base evaluation and treatment upon individual reports rather than gender-based stereotypes." **Binik** points out that "pain and pleasure researchers have something to learn from each other." I cannot say it any better.

Pains, brains, and opium

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Abstract: In this response, I discuss the roles of the peripheral afferent drive in the maintenance of persistent pain, the concept of preemptive analgesia and the importance of the brain, the detailed involvement of which in pain is far less well understood compared to the events in the spinal cord. A comparison of pain to other sensory modalities is then made together with a discussion of learning and pain. These facets of pain are discussed in the light of treatment strategies for this condition.

R1. Introduction

First and foremost, I wish to say how much I enjoyed and appreciated the comments. One of the great joys of science is communication, and these open and frank views, with their benevolent and constructive comments, illustrate the ways in which advances in a subject can occur via interactions as well as by research. It should also be noted that the comments are from both scientists and clinicians. The remarkable advances in the understanding of pain transmission and control that have arisen over the last decade are in no small part due to dialogue and interactions between these two groups. It is difficult to imagine many other areas of neuroscience where science and clinical medicine are so well integrated. However, we are still using opium and derivatives of the bark of the willow to combat pain – it is perplexing that, given the number of targets that there are for the control of pain,

the pharmaceutical industry has not developed a single novel analgesic.

R2. Pain starts in the periphery

Where does one start when discussing pain? Logically, where pain starts, and so to the periphery.

A theme that arises in a number of commentaries is the relative role of peripheral activity and central hypersensitivity in setting the level of pain transmission. **Devor, Gracely,** and **Cleland & Gebhart** all raise this point. The issues here are twofold: (1), whether central hypersensitivity can occur in the absence of peripheral activity and (2), the relative importance of peripheral and central activity in the generation of the final sensations.

Because both the above authors and I believe that central hypersensitivity cannot occur in the absence of peripheral activity (see sect. 7.1), the second point I feel is easily handled. As peripheral activity will go nowhere without central transmission and central hypersensitivity needs peripheral activity, the two are intimately linked. Thus blocking either would be effective. Which would be most effective? The actual levels of activity produced by each is one issue. The points made by the three commentators are important ones. Both **Gracely** and I discuss the effects of combination therapy because, as pointed out by **Gracely,** NMDA antagonists would only reduce the sensitized components. Thus, I feel that an NMDA antagonist plus morphine could be the most effective approach to pain control with centrally acting agents, because spinal opioid analgesia, by virtue of the predominant presynaptic actions of opioid receptors in blocking primary afferent transmitter release, would synergize with the postsynaptic reduction in hypersensitivity produced by NMDA blocker (sect. 7.1). The advantage here is that low doses of each could be used and so reduce side-effect liability.

This approach could provide excellent pain relief in situations of tissue damage. A problem is that in neuropathic states, opioids are less effective and there are as yet no studies in humans on the effects of this combination after nerve injury. Here I refer to the commentary of **Backonja,** who agrees with the point I made that morphine needs to be tried in neuropathic pain patients and the dose escalated to a maximum before other approaches are tried. Jadad et al. have shown that some neuropathic pain patients do well on opioids. The commentary of **Marchettini et al.** on the differentiation of neuropathic syndromes and that on the fact that opioids can work in some situations reinforces these points and lends further support to the idea that lumping together all the varieties of nerve damage is counterproductive. Subdivided neuropathic syndromes may reveal certain symptoms that respond to opiates. Note also (sect. 9) that some measures of behaviour in animal models of neuropathic pain respond to morphine whereas others do not. The same point is made by **Siddall,** to whose comments I will return later in the context of inhibitions.

It is also true that blocking the peripheral activity will be equally efficient, as suggested by **Devor, Gracely,** and **Cleland & Gebhart.** I entirely agree with **Cleland & Gebhart** that the basic studies (paras. 7 and 8) suggesting that hyperalgesia persists after nerve block may well be flawed by technical problems. So, since we all agree on this issue, what would be the best approach? I suppose that with, for example, neuropathic pain, an ongoing local anesthetic block is impracticable so the question remains as to how to block persistent peripheral drives. The recent description of unique sodium channels in small diameter peripheral fibres may be a great target (Akopian et al. 1996) but whether selective blockers can be developed is another question. These agents would not influence allodynia.

R3. Stopping pain before it starts

The implications of the degree of peripheral drive for the concept of pre-emptive analgesia are then developed by **Devor, Gracely,** and **Cleland & Gebhart.** The point about the need for relentless block for acute pain management (**Gracely**) is borne out by our study (sect. 7.2) in which the timing of morphine treatment on the formalin response was used. This is illustrated in Figure R1. I agree entirely with the points made by **Cleland & Gebhart** and illustrated in their diagram. I have been using Figure R1 for talks (a case for parallel evolution?) because it makes the same points but also points out that pre-emptive treatments for tissue injury may also pre-empt beneficial evoked inhi-

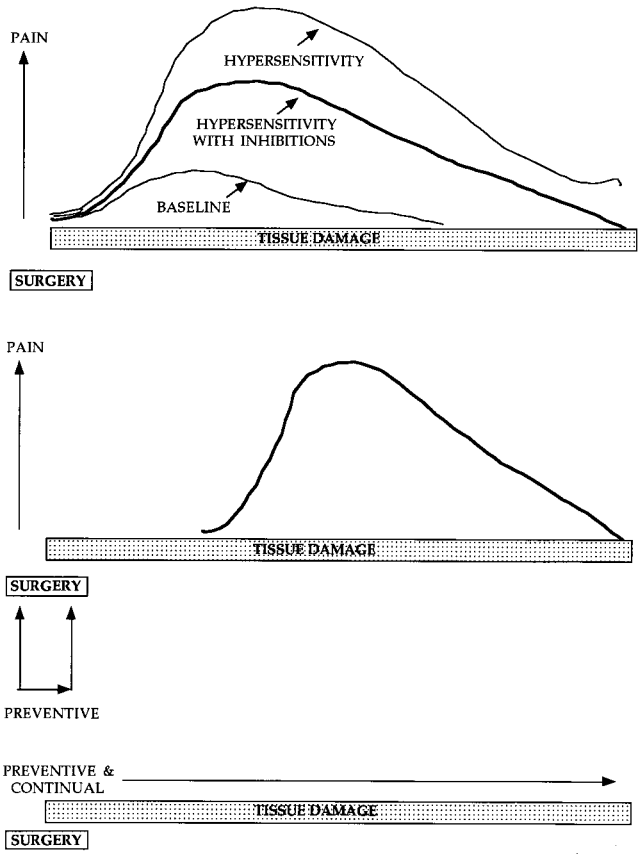

Figure R1. Damage to tissue as a result of surgery (but it could equally apply to inflammation, trauma, or neuropathy) can cause a baseline level of pain transmission that is enhanced by peripheral and central mechanisms of hypersensitivity. The activation of central inhibitory systems will reduce the level of pain transmitted to higher centres. In the second panel, in the presence of continued tissue damage, a short lasting preventive agent (with peripheral or central actions) will only delay the pain that may occur without the compensatory inhibitions, which have also been preempted. The third panel shows how preventive and continued treatment will block all pain until the tissue heals.

bitions (sect. 7.2). Thus there may be a rebound enhanced pain after a short-lasting pre-emptive treatment wears off. In the longer term, patients may do less well if only a brief pre-emptive block is given. There is some clinical evidence to support this premise, as discussed by McQuay (1994).

R4. Pains and brains

Moving centrally into the spinal cord, I indicated that we understand a reasonable amount about the mechanisms underlying plasticity in this first relay in pain transmission. **Hardcastle** and **Watkins & Maier** are right: the brain should not be missing in any overview of pain. **Hardcastle** quotes my remark on supraspinal analgesia, but I accept fully that we need to know much more about pains in the brains. **Benedetti**'s comments also related to these points because he discusses the anxiogenic actions of the peptide cholecystokinin (CCK). It is interesting to note that CCK causes anxiety and reduces analgesia. I accept the point made by **Watkins & Maier** that the term "anti-opioid" is too restrictive, yet the papers they cite on the wider role of CCK in reducing non-opoid analgesia were published only after my target article.

Han has made many important contributions to the research on CCK and I welcome the additional points that he makes in his commentary, all of which I agree with, but I was unable to mention in my target article because of space constraints. **Noble et al.,** although they entitle their account "Clinical perspectives," discuss pharmacological studies in rodents. I presume that the clinical aspects relate to dependence and tolerance. I take exception to their premise that these are problems with the clinical use of opiates such as morphine. There is really no evidence that tolerance is a major problem, since because increased pain can lead to a need to increase the dose, a condition very different from tolerance. Likewise, a psychological dependence leading to drug-seeking behaviour is a very rare event with clinical use of opioids (see McQuay 1997). The rationale for new opioids does not need to include a problem that not only does not exist but is a myth that has hindered the appropriate use of opiates in the clinical use of pain. It may be possible to cause analgesia via manipulation of endogenous opioids, but, as is clear from several of the target articles and commentaries in this *BBS* issue, an opiate that works in neuropathic states would be more than welcome. In this context, CCK antagonists as adjuncts to morphine might do the trick and NMDA antagonists with an opiate or other combinations as mentioned might be appropriate (sects. 5.2 and 7.1).

In response to pain facilitating brain-to-cord messages in inflammation and illness (**Watkins & Maier**), I would respond that this may well occur but the balance is still tilted toward compensatory inhibitions after inflammation. Although there are peripheral, spinal, and centrifugal contributions to enhancement of pain and hyperalgesia these are held down by inhibition. I still stand by my section 7.3 where I suggested that inhibition is increased in inflammation and reduced in neuropathy. Of this point, more later.

R5. Feelings and pain

The affective side of pain is obviously important and occurs in the brain. Yet, the facts that opioids are rewarding and that noradrenaline and 5HT are intimately linked to mood and anxiety, and CCK to anxiety, may be telling us something about the pharmacological modulation of pain and links between the sensory and affective aspects of pain. It is revealing that CCK is reduced after inflammation (less anxiety?) and thus exogenous opioid analgesia is enhanced. In this situation there is increased descending alpha-2 activity and this increase in noradrenergic transmission could elevate mood and analgesia. By contrast, in neuropathy, CCK is increased (anxiogenesis?) and opioid controls are decreased. Add to these the roles of the endogenous opioids and the anxious enkephalin knockout mouse (**Benedetti**), and a common pattern may emerge in which anxiety and pain go together, and euphoria, anxiolysis, and analgesia go hand in hand, the former in neuropathic states and the latter in inflammation. Pathology in the case of nerve damage disrupts both emotions and sensory control; by contrast, after inflammation, beneficial compensations occur. As shown by **Watkins & Maier,** illness and infections can also impinge upon these systems. So, as discussed above, I am convinced of the importance of the higher centres but it is extremely difficult to investigate some of these events with animal studies due to anaesthesia in electrophysiological studies and problems of interpretation in behavioural approaches. The ability to scan the human brain is most likely to provide the impetus to studies of brains and pains. However, it must not be forgotten that the brain responds, in terms of affective and sensory responses to inputs from the spinal cord. The ability of peripheral and central events to substantially alter ascending messages (by increasing or decreasing them) will have a major impact on what messages arrive in the brain and will alter the affective nature of the stimulus.

The peripheral and spinal events are important in their own right, and one need consider only nonmammalian species. The survival value of the response to a noxious stimulus is ancient in evolutionary terms and occurs in very primitive organisms where it is likely to have little or no affective component (Glanzman 1995; Ghirardi et al. 1995). Understanding the first relays is an essential step toward understanding the higher consequences.

R6. Controlling pains

Whilst nestling in the spinal cord, I wish to comment on **Siddall, Clarke, Hu & Sessle,** and **Omote.** The latter comment really reiterates the points I made in sections 4.4. and 7.3 regarding the role of inhibition, both amino-acid and monoamine mediated, and adds some new data. It is interesting to note the enhanced monoamine systems in neuropathic states, which must be the one example of an increase in inhibitions in neuropathic pain. **Omote** mentions the peripheral actions of opioids in inflammation, a topic I mentioned briefly. **Stein & Schäfer** dilate upon this topic from a field of study created almost single-handedly by Stein. I agree entirely that an opioid devoid of central penetration would be an analgesic in inflammation, but I would add that the degree of analgesia produced by this peripheral effect may not be that high and that the control of inflammatory pain is less of a clinical problem than the control of neuropathic pain where this peripheral action may not be so apparent. However, if there is a mixed pain, inflammatory and neuropathic, or inflammation around a

damaged nerve, then this tactic may translate to other pain controls.

Hu & Sessle emphasise that trigeminal mechanisms of pain, of critical importance not only for dental pain but for headache, migraine, and trigeminal neuralgia, may share characteristics with many of the spinal events described. I agree with all of **Hu & Sessle**'s points and read with interest their new findings on the importance of NMDA excitations and GABA inhibitions in the final determination of trigeminal output.

Clarke brings together various strands and we appear to be in full agreement with the idea that inhibitions are a major part of the story. The problem with neuropathic pain (and **Siddall** reinforces this point) is that inhibitions may fail. This may be due in part to neuronal dysfunction (GABA) and in part to a number of other factors (see sect. 5 of original article). Thus, if opioid controls are reduced in neuropathic pains, the approach taken is either to reduce excitations (excitability blockers, membrane stabilizers, and anticonvulsants) or to enhance monoamine inhibitions by the use of antidepressants. **Clarke**'s points reinforce my own about the complexity of the descending control systems. However, the number of receptors and the important point made by **Clarke** regarding the opposite effects on motor control means that the chances of producing novel drugs with selective effects on pain is actually quite high.

In addition to the monoamines, GABA could be a target (**Siddall**) and the benzodiazepines may be one way to enhance inhibitions. However, as we have recently argued, their use depends on the state of $GABA_A$ receptor mediated controls. Benzodiazepines enhance GABA function. If, as might well be the case, GABA controls are increased after inflammation, there could be very little increase that benzodiazepines could induce. Furthermore, in neuropathic pains, if, as several of us have mentioned, there is a loss of GABA controls, possibly due to neuronal dysfunction, then there will be no GABA tone to be augmented. Controlled clinical studies on the use of benzodiazepines are needed. We have recently reviewed this area of pain research (Dickenson et al. 1997).

R7. Learning about pain

The final area covered by the commentaries is that of pain and learning. **Birbaumer & Flor** make a number of points, several of them already addressed earlier in this Response. Yes, the higher cortical processing of pain is critical and memories may well be established as a result of painful experiences, as well as compatible processes occurring in other sensory modalities. Not only may tinnitus be a facet of this but we need to consider hallucinations and agnosia as part of a wide spectrum of pathological and drug induced alterations in the processing of sensory events in the world around and within us. I gave the details of combination therapy for pain because of the multiple pharmacology of the systems; I and several others (see sect. R2) feel that there is no central processing without peripheral drive.

The exception to this is central pain. I did not cover this area because almost nothing is known about it. However, it may not be correct to consider pain as simply another sensory modality. As **Hardcastle** in particular points out, there is a major psychological component to pain, and in most people, this is unpleasant. Other sensory modalities, visual and auditory (see **Birbaumer & Flor**), are neutral. These modalities do not elicit a withdrawal reflex either. The survival value of the stimulus is ancient in evolutionary terms and occurs in very primitive organisms, as mentioned earlier. Learning in response to a noxious stimulus can be demonstrated in aplysia, which has only a few hundred neurones, but even here, the events are sufficiently complex (Glanzman 199; Ghiradi et al. 1995).

Hole et al. discuss learning with regard to noxious inputs, but although enhanced responses can occur in response to an intense stimulation, I feel that the role of inhibition in controlling these events is of utmost importance. The four studies **Hole et al.** cite include two in slices where most inhibitions may be severed, a neonatal cord, where inhibitions have not matured and excitations are greater, and an adult anaesthetized rat. Yes, central enhancement of incoming messages could be viewed as a form of learning, but under these circumstances we find almost exactly the same results as Randic. Not all spinal nociceptive neurones are facilitated; a number show reduced responses after peripheral inflammation, indicating compensatory inhibitions (Stanfa et al. 1992). In fact, **Hole et al.** only mention one facet of hippocampal function, long term potentiation (LTP [see also: Shors & Matzel: "Long-term Potentiation" *BBS* 20(3) 1997]). It is clear that in addition to this prolonged potentiation there is also short- and long-term depression and short-term potentiation. The latter is common in the spinal cord and depressive mechanisms are likely to hold the former in check. Again, in the marine mollusc, both short- and long-term potentiation can occur and inhibition controls the extent of potentiation (Fischer & Carew 1993; Ghiradi et al. 1995). As proposed in section 7.3, if these inhibitory mechanisms function normally in the mammalian spinal cord, pain is held in check, a sensible *modus operandi* for a sensory system. In neuropathic pain, where inhibitions may fail, the long-term hyperalgesias and allodynias dominate. It would be pointless to have a system in the spinal cord in which the gain is routinely shifted upward for many days after a brief stimulus.

R8. Conclusions

Pain is a sensation that is handled differently by the central nervous system depending on the nature of the stimulus (affect, reflex-induction, and commonness). The mechanism of peripheral and central sensitization are much more common and widespread than, for example, tinnitus. Most humans experience many acute pain states where either or both of these events are likely to occur (sprained ankles, sunburn, childbirth, dental surgery, etc.). I appreciate the comments of **Birbaumer & Flor** but feel that pain is more than just another sensory event. There are parallels with other sensory events and other forms of learning but pain stands alone as a sensory system. It can be amplified at peripheral and central sites, where the level of transmission is controlled by inhibition and where the net end result is unpleasant. As a result of a series of events at peripheral, spinal, and higher levels, people suffer pain, they do not simply perceive it.