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Discussion on the Session on Endogenous Antinociception: Report by R. G. Hill

The Royal Society

Phil. Trans. R. Soc. Lond. B 1985 **308**, 403-405
doi: 10.1098/rstb.1985.0040

Phil. Trans. R. Soc. Lond. B **308**, 403–405 (1985)
Printed in Great Britain

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This session examined the concept of endogenous inhibitory systems that act to modulate nociceptive inputs. In particular, the role of descending pathways and the identification of neurotransmitter candidates were stressed. The nature of the presumed inhibitions was also elaborated on as far as was necessary to decide whether they were tonic or phasic in character and whether they acted presynaptically or postsynaptically or possibly even without benefit of classical synapses.

In discussion, the nature of raphe spinal inhibition received considerable attention. It was pointed out that among other things this pathway served to inhibit motoneurons and that a myelinated pathway (conduction velocity up to 15 m s^{-1}) was involved, arguing against a role for the 5-hydroxytryptamine containing fibres classically associated with the physiological functions of the raphe nuclei. It was possible that attenuation of behavioural responses by electrical stimulation of the brain stem was, in fact, attributable to suppression of motor outflow rather than of sensory input, although no evidence was presented that excluded either alternative under the appropriate experimental conditions. Indeed, one feature of this discussion period was the recognition by separate groups working in this field, that their results differed quite considerably, and that these disparities could not always be explained away in terms of obvious factors such as species differences. It became clear that there were many permutations in experimental design and the obvious criticism was made that we were collectively attempting to oversimplify the situation. This point met the rebuttal that it was necessary to be able to do experiments and therefore conceptually simple working hypotheses were needed.

An important matter not mentioned in the formal presentations was the role of descending inhibition triggered as a result of intense afferent input. It was stressed that one result of such an inhibition could be to turn off a low threshold input in a selective manner and thereby allow the central nervous sytem to more readily appreciate a high threshold (and presumably nociceptive) input. It was therefore wrong to infer that descending inhibitory processes were always likely to be antinociceptive.

The role of tonic descending inhibitions (which were admitted to be a possible consequence of trauma in the surgical preparation of the experimental animals) was not fully elucidated. Lesions of sites in the medulla appeared to abolish such inhibitions but it is not yet clear whether the effective lesions are of cells of origin or of fibres 'en passage'. Examination of the supposition that tonic inhibitory processes might be activated by surgical or traumatic injury raised the question of whether the input resulting from injury had itself to be tonic or whether there was a 'switch-on' phenomenon at the time of injury. The simple expedient of sectioning a dorsal root serving the area of injury during the course of an experiment in order to produce an effect analogous to that resulting from cold block of descending fibre tracts did not seem to have been attempted. This then lead to the accusation that as patients undoubtedly did feel their pain then this line of investigation was fruitless, although the possibility that a more severe pain might be experienced in the absence of such tonic descending inhibitions was neglected.

The involvement of different neurotransmitters in the effects described received lively discussion, much of it centred on the involvement of endogenous opioids. There was obviously some disparity in the observations made by different groups on the effects of the opioid antagonist naloxone. Even accepting that it was possible to show that a naloxone-sensitive descending inhibition onto dorsal horn neurons did exist, there remained the problem of interpreting the experimental observations. The inadequate specificity of naloxone and other antagonists was raised as was the need to remember that the production of analgesia was but one facet of the complex pharmacology of both exogenous and endogenous opioids.

The actions of naloxone on motoneurons was an interesting case in point and as yet it is not possible to infer which opioid receptor subtype(s) is (are) implicated. The question as to why administration of naloxone did not produce rigidity either clinically or in conscious animal experiments was raised. This was explained by the lack of tonicity in opioid operated inhibitions and evidence for spinal [Met]enkephalin release only in response to C fibre afferent volleys was cited. The physiological rationale for opioid operated inhibition of motoneurons was suggested to be a means of producing immobility in the presence of an intense nociceptive input. It was interesting to note that a similar opioid-operated inhibition could be demonstrated to act upon sympathetic outflow.

The lack of specificity in pharmacological tools also received attention during the discussion of the so-called GABA-mimetic analgesia produced by THIP. Recently it had been shown that this analgesia could be blocked by muscarinic receptor antagonists and thus may be explicable in terms of the muscarinic analgesia story that was in vogue before the discovery of the endogenous opioids.

Discussion of future trends in pain research moved outside the topic of synaptic inhibition but retained the theme of chemical messengers. It was asked what was special about afferent C fibres and in particular whether their peptides functioned as trophic factors. The observation that Aδ fibres performed the same impulse-carrying role as C fibres, but rather better, raised the query as to why all mammalian species have a majority of unmyelinated fibres in their peripheral nerves. The point was well made that some cases of chronic insensitivity to pain had depleted C fibres in peripheral nerves and some did not. This may have relevance to the observation that in animal experiments where C fibres are killed off with neonatal capsaicin treatment then changes in A fibres are also seen.

The loose use of the term trophism received criticism as this should be confined to processes occurring from days to weeks after injury and could not adequately describe events happening within minutes (although some chemical processes, e.g. glycogen phosphorylase activity could change that rapidly). The role of classical neurotransmission was also considered. A number of peptides that were present in C fibre afferents including substance P and vasoactive intestinal polypeptide (v.i.p.) were capable of exciting dorsal horn neurons and although 'slow' in action compared with, say, excitatory amino acids, did not have a time course of effect extending into minutes, days or weeks. These substances did fulfil the criteria (e.g. Ca^{2+} dependent release) that were normally associated with neurotransmitter function and thus there was no need for their role to be re-categorized.

The discussion then moved onto the problems of long-lasting clinical pain as exemplified by arthritis and by cancer. The question of the involvement of peripheral nerve damage in such chronic pain was raised and it was noted that in some intractable cancer pain then nerve involvement was observed. It was also pointed out that normal nerves might become damaged

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in some way by an abnormal level of impulse traffic. The action of capsaicin was again used in illustration of the dissociation of chemical and electrical roles of afferent C-fibres. In adult animals soaking a peripheral nerve in a capsaicin solution produces, after two weeks, a failure of neurogenic vasodilation but apparent preservation of impulse traffic in the unmyelinated fibres of the nerve trunk.

The general discussion moved into more philosophical realms and it was salutary to note that the organizers had not been able to locate a speaker to cover the philosophical issues as part of the formal programme! Two schools of thought were in evidence among the discussants, namely those who considered that pain is an entirely human experience and those who maintained that the behavioural reactions of lower animals were adequate to infer that they felt pain too. It was generally agreed, however, that the behavioural repertoire of spiders and worms was somewhat inadequate for this purpose. The role of emotion in pain perception received justifiable criticism when it was pointed out that music and visual arts could also evoke emotional responses but this was attributed to the brain rather than to some special property of the eyes and ears.

The definition of pain ranged from 'a body image projection on the cerebral cortex' to a reflection of 'that psychical act called sensation'. The old chestnut of 'brain' versus 'mind' was raised but the meeting was reluctant to admit that there were matters of the mind that were inexplicable. The function of pain was introduced as an extension of a protective mechanism that served via reflexes to produce immobility and impinged on consciousness as a bonus.

The absence of an ethically acceptable animal model for chronic pain conditions was a matter of general agreement and those who worked with arthritic rats were emphatic that the nociception experienced by these animals was essentially acute and related to some stimulus applied to their abnormal joints. It was also stressed that in certain situations (e.g. thalamic syndrome) pain that was undoubtedly real to the patient could occur in the absence of nociception as such.

It was also well documented that previous pain experience could lead to 'memory pain' when a suitable sensory stimulus was provided. There was speculation about the role of learning processes and the production of reverberatory circuits leading to the manifestation of chronic pain symptoms, but no hard evidence is yet available.

The meeting concluded with an abiding impression that much was left to discuss and that this would be a fertile field of research for many years.

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