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Discussion on the Session on Nociceptive Systems: Report by P. M. Headley

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Discussion on the session on nociceptive systems: report by P. M. Headley

This session was concerned with *in vivo* studies on acutely prepared animals. Among other topics, one important issue was raised several times but in somewhat different guises: namely to what extent are the neuronal receptive field properties detected in such experiments influenced by *general* changes of the excitability either of the recorded cell or of cells earlier in the sensory pathway? In this context excitability can be altered either by increasing sensory inputs, as with tissue damage, or by depressing central activity as with general anaesthetics; and it seems to this reviewer that such changes should be distinguished from more specific excitatory or inhibitory mechanisms triggered by particular synaptic inputs such as those discussed by Professor Matthews. In this session the issue of excitability was raised in questions to Dr Guilbaud on altered thalamic cell properties in rats that have an increased sensory input from arthritic joints; again with respect to the effects of general anaesthetics on the cortical nociceptive responses described by Dr Andersson; and, indirectly, in questions to Dr Cervero on viscero-somatic convergence onto spinal neurons.

As was suggested from the floor, one means of alleviating part of the problem is to use a variety of anaesthetics that interact differently with neurotransmitter systems; but Dr Andersson was quick to point out that, as would be expected, most general anaesthetics abolish cortical nociceptive inputs, even at low doses. Another possibility, also raised from the floor, is to increase the excitability of the cell under study to a predetermined level with a microelectrophoretically administered excitant: by this means those synaptic inputs that are subliminal under the particular recording conditions of the time can often be revealed and may substantially alter the experimenter's classification of the receptive field properties of the cell. By keeping to a standard protocol, this technique also allows more direct comparisons between control and test situations.

A further important complication of acute electrophysiological experiments *in vivo* was raised by Professor Matthews's report that trigeminal neuronal responses to tooth-pulp stimuli are tonically inhibited by sensory inputs generated by the preparatory surgery and mechanical immobilization of the animal. That neuronal responsiveness can be grossly distorted in this way by the experimental conditions clearly concerned many of those present; but, as was pointed out, Professor Matthews's results parallel other experimental findings that high-intensity electrical or natural stimuli can generate body-wide inhibitions of nociceptive responses in spinal and trigeminal systems.

One interesting possibility raised on this topic was that there could be a common aetiology between Professor Matthews's reported inhibition in the trigeminal system and tonic 'descending' inhibition; the latter, which can be readily demonstrated in acute preparations by reversible spinalization, is relatively selective for nociceptive as opposed to other spinal responses. As pointed out, neither type of inhibition is naloxone-reversible, although some other forms of stimulus-evoked inhibition of nociceptive responses are naloxone-sensitive, albeit in a species and laboratory-selective manner.

To what extent different sensations and different qualities of pain arising from tooth-pulp

stimulation can be discriminated was raised both in Matthews's talk and in the ensuing discussion. Professor Matthews emphasized the technical problem of avoiding the spread of stimulus from tooth-pulp to periodontal areas, whether the stimulus be electrical or thermal (particular care should be taken when using electrical stimulation of rat teeth). He concluded that man cannot perceive warm or cold sensations from tooth-pulp, although it may be possible to discriminate between the pain produced by hot and cold stimuli; and indeed, in cats the differential information is known to be present in primary afferents.

Professor Matthews was also prompted to point out that the jaw-opening reflex, which can be readily elicited by tooth-pulp stimulation in experimental animals, and which is often taken as an index of nociceptive responsiveness, is different in man; thus there is no contraction of jaw depressor muscles, just a reduction of any pre-existing elevator muscle activity. The threshold of this response correlates with the first detectable sensation, and not with the threshold of pain.

Dr Cervero's assertion that there are specific (as well as non-specific) nociceptors in the gall bladder, biliary duct and other viscera came under question, no doubt because there were several in the audience who have experience of urinary bladder receptors; the latter (along with various gastrointestinal and cardiovascular receptors) appear to form a uniform population, which respond progressively from normal physiological to noxious levels of stimulus. At present it is most likely that there are genuine differences between viscera, although the possibility must remain that some or most viscera do have more than one receptor type responding to noxious stimuli, but that these receptor populations are sampled differentially in the technically very difficult experiments in which single C fibres are recorded and characterized.

The site and nature of viscero-somatic convergence was also raised. Although it is clear that there is some preganglionic convergence (the poster by Taylor, Pierau & Mizutani addressed this question), Dr Cervero suggested that the proportion of such cells with branching peripheral processes was small and that the ability of second order spinal neurons (and indeed of whole animals) to differentiate visceral from somatic stimuli indicates that not all visceral afferents also convey somatic information. Much of the convergence must therefore be spinal, although quite what converges with what must remain an incompletely answered question; this may depend on mean levels of interneuron excitability, as discussed above, as well as on the descending excitation (originating at least partly from the raphe nuclei) and inhibition to which these spinal cells are subject.

In answer to a query about the rostral projections of spinal biliary nociceptive neurons, Dr Cervero stated that less than 10% of his sample had detectable rostral projections, but that this limited number mostly projected into contralateral spinothalamic or spinoreticular tracts rather than into ipsilateral spinocervical or dorsal column postsynaptic pathways.

As reported above, Dr Guilbaud's talk precipitated a discussion on the effects of altering cell excitability. In addition, she was prompted to say that acute injections of carrageenan into the foot could alter thalamic receptive field properties in a manner similar to that reported for spinal cord by McMahon & Woolf in their poster; and the latter authors have shown that the changes are *not* simply the result of increased primary afferent input from the injured area.

The effects of morphine and naloxone on thalamic neurons generated several queries, to which Dr Guilbaud emphasized that morphine was highly effective in both normal and arthritic rats at low doses (10–100 $\mu g\ kg^{-1}$). More surprisingly, very low doses of naloxone (1–10 $\mu g\ kg^{-1}$) depress responses in arthritic rats with a potency about ten times that of morphine; and Dr

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Guilbaud sees similar anti-nociceptive effects with these doses in the rat paw pressure vocalization test. Furthermore, in the thalamus these low doses of naloxone are additive with morphine, although higher doses (100 μg kg^{-1}) of naloxone do antagonize morphine actions in the traditional manner.

In reply to a further question, Dr Guilbaud said that the depression by intravenous aspirin of thalamic nociceptive responses in arthritic rats was paralleled (in her experiments with Professor Iggo) by a reduced sensory discharge from arthritic joints; this should not, however, be taken to prove that aspirin does not have additional central effects.

After his talk, which was the last in this session, Dr Andersson was pushed to specify which layers in somatosensory cortical areas I and II might be responsible for discriminating 'pain' information; but he emphasized again that such conclusions are hard to draw at present because of the extreme degree of spatial and/or modality convergence of excitatory inputs to this and neighbouring areas of cortex. The only clues to discrimination lay in the localized presence, especially in layer IV, of noxious stimulus-related inhibitions.

The audience was invited by another contributor from the floor to offer any available information on the possible physiological relevance of the high levels of κ opiate receptor binding, which have been described in layers V and VI of widespread areas of cortex; but the audience proved to be either ignorant or reticent about this matter.

A final and interesting question raised the point that cells in many cortical areas – most notably in the primary visual cortex – respond only to stimuli that are very tightly specified in terms of intensity, size, orientation, etc. There appears not to be any such area for pain sensations. In the eyes of this reviewer, this finding supports the notion that nociceptive and pain information is often processed, from primary afferent through to cortical levels, in a manner rather different to that employed in the processing of inputs of other general and special senses.

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