

An approach to pain assessment in the laboratory setting

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Pain is unpleasant, an adverse sensation that plays an important role in human life. Humans are able to express their negative feelings about painful stimuli by body language and vocalization. Behavioural studies in animals have clearly shown that they have similar reactions to stimuli that are painful to humans, indicating that such stimuli are also painful to animals. The importance of pain sensation to the well-being of humans and animals lies in the fact that pain makes the individual alert to potential tissue damage. But because pain is also an adverse sensation, it is also a hindrance to well-being. The development of methods to diminish pain in humans and animals has become an important issue in medical sciences. In contrast to the universally recognized importance of preventing the sensation of pain, the definition of pain has been controversial for many years. However, pain defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" is today accepted as a working concept by the International Association for the Study of Pain (IASP). Yet the objective quantification of pain, in humans as well as in animals, remains complex.

Two PhD theses [1] [2] have addressed the physiology and pharmacology of pain in rats. The studies focussed on the brain's response to pain, rather than on spinal cord reflexes, since the observed effects in the spinal cord models (relaxation on anaesthetic drugs administration) are not conclusive for pain perception. Pain perception is an exclusive function of the brain. The first of these two studies determined the pathway for pain through the rat's brain and both theses examined the effect of pain on the rat's brain by studying the sensory effect of a stimulus. By combining the rat's emotional response together with the sensory response to the stimulus, the effect of the stimulus could be defined as pain. In both studies the investigators were able to show a quantifiable relation between the increase in the noxious stimulus and the effect on the rat's brain. The aim in both theses was to quantify the effect of a defined noxious stimulus on the rat's brain and to modulate that effect by administering a quantified dose of a defined anaesthetic agent.

Electrophysiological methods were used because they make it possible to quantify the stimulus as well as the effect, the evoked potential. An evoked potential is an electrical manifestation of the brain's reception and response to an external stimulus. Somatosensory-evoked potentials are those evoked by short stimulations of peripheral somatosensory nerve fibres. A variable electrical stimulus was administered at the base of the tail and the somatosensory-evoked potential (SEP) was recorded from the dura mater adjacent to the skull. Part of the first thesis was devoted to defining the most reliable site for recording the SEPs. The electrical stimulus was not discriminately applied to specific sensory nerve fibres—tactile-processing (pertaining to touch) or nociception-mediating (pertaining to pain sense)—of the tail but to the epidermis at the base of the tail. To enable recognition of the nociceptive component in the response SEPs, the rats were given variable doses of fentanyl, a μ -opiate receptor agonist. This modulates and thereby reveals the nociceptive component, while not affecting the tactile component. Two different responses were recorded at two locations on the skull, one on the vertex (Vx-SEP) and the other over the primary somatosensory cortex (SI-SEP).

Both of these theses aimed at defining the physiologic character of the two different SEPs and determining which of the two responses was the more suitable for evaluating pain and the effect of analgesic drugs on pain sense. One component of the Vx-SEP, with a latency of 15 ms, proved to be highly sensitive to both increased stimulus frequency and different anaesthetic drugs, which suggests that it represents a primary somatosensory mechanism to discriminate between relevant and irrelevant stimuli. This makes it especially useful for studies of nociception and analgesia. This component, designated as Vx-SEP P15, was further tested with respect to its potential as an indicator of analgesic efficacy.

A Pavlovian fear-conditioning model was used to establish the correlation between Vx-SEP P15 and animal pain. In Pavlovian fear-conditioning, animals learn that an innocuous (non-painful) stimulus precedes and thus predicts a painful stimulus. The rat reacts to the painful stimulus with fear, that is,

the behavioural fear-reaction of being startled, which can be analyzed and quantified. After the rat has been conditioned, the innocuous stimulus alone will startle it. This fear-conditioned behaviour is considered to be a measure of the rat's emotional experience to the painful stimulus. The emotional component of pain is therefore included in the pain model, thus satisfying the IASP definition. Using this model, it was suggested that the Vx-SEP P15 is involved in discriminating between relevant and irrelevant nociceptive stimuli and is thus potentially useful for assessing the efficacy of analgesia. The second thesis [2] proceeded with a further study of the relation between the SEP and the fear-conditioned behaviour under various circumstances, with the aim of establishing the reliability of the SEP during increasing stimulus intensity and different analgesics.

The overall and most important conclusion of these studies is that pain can be measured in rats and that analgesics are proved to diminish the pain. The methods used in these studies are elaborate and not yet directly applicable to the measurement of pain in an individual animal under veterinary care. The methods used are, however, now suitable for study of the efficacy of analgesics in rats. When analgesics have a sedative effect and an analgesic effect, a dose-dependant study is needed to establish analgesic efficacy. It is a leap forward to be able to measure pain and anaesthesia in animals and further studies along this line should be encouraged. The basic work is done and the findings should now be applied to evaluate pain in the individual animal objectively. However, the methods described in these theses under laboratory conditions must first be modified in order to measure pain in individual animal patients.

References

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