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Title : EXPERIMENTAL HYPERALGESIA: MODEL FOR CLINICAL PAIN?

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Introduction. Hyperalgesia is a common outcome of tissue injury and inflammation. In the present study we experimentally induced hyperalgesia in humans by applying noxious heat or noxious chemical substances to the skin. We measured, psychophysically, pain sensations evoked by local heating of the skin before and during hyperalgesia. The results obtained were compared with responses to the same stimuli of single nociceptive afferents in monkeys. Our purpose was to determine which aspects of hyperalgesia might be attributable to neural events at the level of the peripheral receptor and which aspects reflect transformations of these events within the central nervous system.

Methods. Human subjects, each of whom gave informed consent, were tested under a university approved protocol. In psychophysical scaling experiments, subjects made continuous ratings of the magnitude of pain sensation evoked by brief thermal test pulses, applied to the volar forearm, of 0.1°C to 13°C each superimposed on a 38°C or a 28°C base temperature. Pain threshold was defined as the minimal temperature evoking pain on 50% of the stimulus presentations. Experiment I determined the time course in development of heat induced (HI-) hyperalgesia. Magnitude ratings were obtained from 6 subjects before and at varying intervals of time after a conditioning stimulus (CS) of 50°C, 100 sec duration. Similar stimuli were applied to the cutaneous receptive fields of single nociceptive afferents and low-threshold thermoreceptive afferents found in peripheral nerve of monkeys who were anesthetized by sodium pentobarbital. Electrical signs of activity in single afferent fibers were recorded via the method of single unit analysis. In experiment II, capsaicin-induced (CI-) hyperalgesia was studied psychophysically. A 1% solution of capsaicin (Sigma Chem. Corp.) was topically applied to a small region of the skin in 3 human subjects. Pain ratings of thermal stimuli were obtained prior to application of capsaicin and again 1.5 hours after, when the erythematous reaction appeared to reach a maximum.

Results. I) The time course in development of HI-hyperalgesia. Prior to the CS the pain threshold averaged 45°C on the 38° or 28°C base. Immediately after the CS, pain ratings of suprathreshold stimuli were reduced and pain thresholds elevated by 4°C; but by 5 min. after the CS, ratings were increased above normal and pain thresholds lowered to 41°C (38°C base) or to 38°C (28°C base). This state of hyperalgesia remained for several hours. The magnitude and time course of these changes in pain sensitivity were paralleled by analogous changes in heat thresholds (minimal heat intensity evoking one or more nerve impulses) of C-fiber polymodal nociceptors (CPNs) in monkeys following a similar CS and test stimuli. In contrast, hyperalgesia could not be accounted for by alterations in the heat sensitivities of either low-threshold cold or warm receptors or A-fiber mechanoheat nociceptors following the same CS. During the hyperalgesic state human subjects reported an unpleasant sensation evoked by lightly rubbing the skin with gauze. Analogous changes were seen in the increased sensitivity of certain CPNs to mechanical stimuli. Some CPNs also increased their responsiveness to noxious cold following the CS. II) Sensory alterations following CI-hyperalgesia. Within one hour following application of capsaicin, spontaneous, burning pain appeared within the erythematous area and an unpleasant sensation was evoked by lightly stroking the skin or by moving single hairs. Hyperalgesia remained for up to 18 hours. Pain threshold to heat was greatly lowered to 31° (on 28° base) and increments of 0.25°C were detected as painful on the 38° base - the latter rated as continuously painful. There was complete temporary relief from spontaneous burning pain and a transient return to normal thresholds for mechanically evoked pain after immersion of the affected area of skin in cool water. However, water that was painfully cold to normal skin evoked more pain in capsaicin-treated skin.

Discussion. The sensory alterations in HI- and CI-hyperalgesia resemble those occurring as a result of tissue injury and inflammation; namely, increased pain evoked by noxious heat or cold stimuli, and a painful response to normally innocuous stimuli such as gentle warming or lightly rubbing the skin. Results analogous to these, obtained in recordings from C-fiber polymodal nociceptors in the monkey, suggest that alterations in pain thresholds and other sensory abnormalities in hyperalgesic skin following heat injury are largely determined at the level of the peripheral receptor. Analogous studies of the responses of nociceptors following application of capsaicin remain to be done.

Experimental studies of pain are traditionally carried out in normal skin. However, in many clinical conditions pain is associated with inflammation or tissue injury, where chemical mediators are released and may act to increase the excitability of nociceptors. In this context, experimentally induced hyperalgesia in the skin may provide a better model for studies of clinical pain and provide a better means of evaluating the therapeutic actions of analgesic drugs.