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DEVELOPING CONCEPT OF THE GATING MECHANISMS IN PAIN PERCEPTION

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Abstract. A short review of the main trends in neurophysiological research of the gating mechanism of pain perception is presented. The original model of Melzack and Wall has been modified in two aspects. First — postsynaptic inhibition and increased concentration of potassium ions in the extracellular space play a role in the modulation of impulse transmission at the segmental level of the spinal cord. Second — serotoninergic descending pathways originating in the medial structures of the brain stem which are very sensitive to narcotics contribute to the modulation of synaptic transmission from noccieptors.

Pain is an unpleasant, sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (3). We can recognize three sides of subjective appreciation of pain (1): First, pain is an evidence of body damage, second, pain has an emotional, or affective side. These two are common for both the animals and the humans. The third, the meaning of pain, is specific for humans. Only the human can estimate the real meaning of pain on the basis of his education.

In spite of a significant progress in the research of neuronal mechanisms of pain we are realizing that our knowledge consists only of

individual findings, or clusters of findings, and that for the formulation of a neurophysiological concept of pain we still have to utilize our imagination or speculation to a great extent (for excellent reviews see 8, 27). As an apology for not making a fast enough progress, we have to say that experimental research has been hampered by two facts: first, that only humans can communicate and express verbally the subjective phenomena, while in animals we can pronounce judgements on pain only from their behavior and we are frequently uncertain in estimating whether the effects of various analgetic procedures change only reflexes, evoked by nociceptive stimuli, or do as well alleviate pain (20). Second, there is no other field of research which is so close to the limits of our ethics as is experimentation on pain in animals and great care has to be taken that the scientific profit should really compensate for the deficits in ethics (7).

The nociceptors, i.e. the afferent fibers which conduct impulse activity, evoked by stimuli that are damaging body tissues, or close to it, belong to the slow conducting group A-δ, exhibiting conduction velocity up to 40 m/s and to the group C which consists of unmyelinated nerve fibers, exhibiting conduction velocity of less than 1 m/s. The nociceptors respond to various kinds of noxious stimuli, e.g. thermal (above 45°C), or mechanical (above 40 g/mm^2). The fibers of the group A-α and β which possess a lower threshold and exhibit conduction velocity of 100 m/s, can be stimulated with electrical pulses of up to 1,000 Hz without eliciting pain (2).

At the trigeminal level special attention was paid to the tooth pulp nerve because it consists solely of A δ and C fibers and pain is the predominant sensation which can be evoked by selective stimulation of the tooth pulp in humans (16).

Melzack and Wall (13) suggested that large afferent fibers inhibit transmission to the second order neurons in the spinal cord, while the small afferent system, predominantly the unmyelinated C fibers, facilitate it (Fig. 1). This suggestion, based on the assumption that nociceptive stimuli induce hyperpolarization of the primary afferent fibers and should therefore result also in presynaptic facilitation (14), has not been confirmed by several groups of neurophysiologists (6, 21, 26). These found that selective stimulation of C fibers produces depolarization of the primary afferent terminals of the spinal cord, similarly to the large fibers. However, in spite of the shortcomings in physiological premises, the main idea of a gate for the transmission of impulse activity induced by nociceptive stimuli proved to be correct, but the gate mechnisms turned out to be much more complicated than it was throught at the beginning (15).

The research which followed greatly extended the knowledge on the mechanisms that may be involved in gating the impulse transmission from nociceptors. Liebeskind, Mayer and Akil (12) demonstrated that prolonged electrical stimulation of the periaqueductal gray of the brain stem produced analgesia without any obvious changes in the behavior of the animals. Since then evidence has been accumulated which makes it likely that the serotoninergic neurons in the nucleus raphe magnus form the descending pathway which inhibit the impulse transmission from peripheral nociceptors at the level of dorsal horns (5). Local application of small doses of morphine (0.3 μg) to periaqueductal gray and to the nucleus raphe magnus, results in an appreciable increase of the pain threshold for nociceptive stimuli (4, 24). It is thus reasonable to assume that in these regions which apparently play a key-position in the perception of pain opiate receptors are incorporated in the membranes of a class of neurons. This idea was corraborated by the discovery of endogenous ligands to opiate-receptors, enkephalins and endorphins, which exhibit an analgetic effect similar to that of narcotics (9) (Fig. 2).

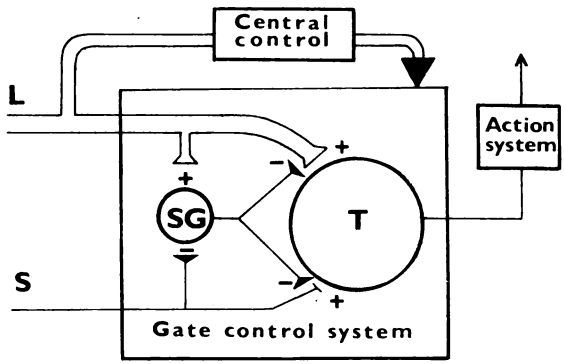

Fig. 1. The gate theory of Melzack and Wall (13). L, the large diameter afferent fibers (A-β); S, the small-diameter afferent fibers (C and A-δ). The fibers project to the substantia galatinosa (SG) and first central transmission cells (T). The inhibitory effect exerted by SG on the afferent fiber terminals is increased by activity in L fibers and decreased by activity in S fibers. The central control trigger is represented by a line running from the large fiber system to the central control mechanisms. These mechanisms, in turn, project back to the gate control system. The T cells project to the entry cells of the action system. +, excitation, —, inhibition.

What is the present model of a neuron engaged in producing analgesia? The neuropharmacologists suggested that a neuron possesses at least two kinds of receptors which are so closely connected that they

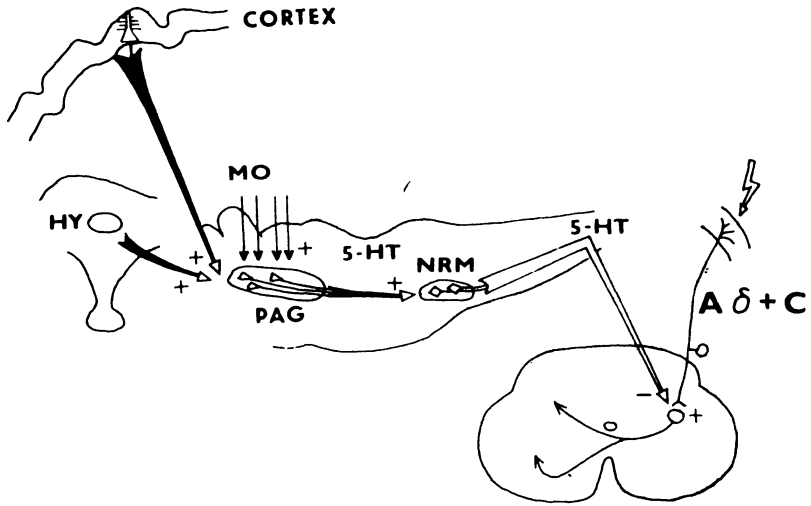

Fig. 2. System of descending pathways inhibiting transmission from nociceptors. Hy, hypothalamus; PAG, periaqueductal gray; 5-HT, 5 hydroxytryptamine; NRM, nucleus raphe magnus; MO, morphine; +, indicates excitatory, —, inhibitory action; A, delta and C indicate small diameter afferent fibers.

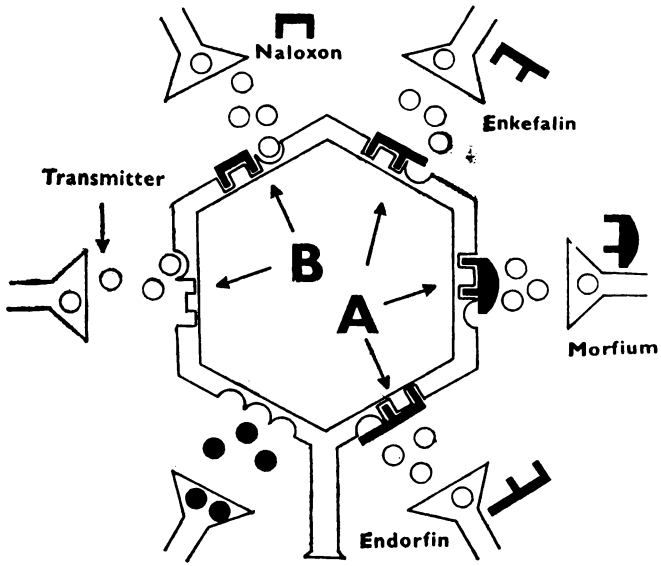

Fig. 3. Model of the action of opiates on a neuron within the pain system. Opiate receptors in the cell membrane are represented by two squares which can be occupied by morphine, enkephalin, endorphin and naloxone. Receptors for the transmitters are represented by half-circles. The excitatory transmitter is represented by open circles and the inhibitory transmitter by closed circles. Analgesia (A) results when opiate receptors are occupied by a molecule which exceeds its size and prevents interaction between the excitatory transmitter and its receptor, but not in *B*. The neuron can also be inhibited by direct action of inhibitory transmitter.

form one complex (Fig. 3) (25). One of the receptors in the complex can be activated by a transmitter leading to depolarization of the neuron and to its discharging, or to hyperpolarization and its inhibition. The other can be occupied by morphine, or by endogenous ligands of opiate receptors (enkephalines and endorphins). The molecules of morphine, metenkephalin and endorphin do not fit the opiate receptor exactly and prevent the interaction of the excitatory transmitter and its receptor at the postsynaptic membrane. The action of naloxone, which prevents analgetic effects of morphine, is explained by high affinity and exact fitness of its molecule to the opiate receptor, so that it leaves open the way for the excitatory transmitter to its receptor at the postsynaptic membrane. The events *A* in Fig. 3 thus result in analgesia, but not those indicated as *B*.

It has been suggested that the release of endorphins may be the underlying mechanism of the analgetic action of various types of electrostimulation (17). However, it has to be kept in mind that tetanic stimulation of peripheral nerves results in accumulation of potassium in extracellular space at the segmental level of the spinal cord, which was shown the modify the impulse transmission (11, 23). The records in Fig. 4 demonstrate changes in potassium concentration in the extracellular space of the spinal cord of the cat as measured with potassium sensitive microelectrodes (10). It can be seen that the potassium concentration can increase twice or even three times its resting level, which results in appreciable depolarization of the glial and neuronal elements. Although the physiological role of the increased $(K)_e$, arising during neuronal activity, is still under investigation (18, 19), it is already clear that at the concentration higher than 6 mmol/1 it inhibits impulse transmission from afferent fibers (22).

Figure 5 summarizes the data and represents a model of neuronal and humoral mechanisms which may contribute to analgesia by suppressing impulse transmission from nociceptors at the segmental level of the spinal cord. The following mechanisms can be listed: (1) Presynaptic inhibition which is probably weak. (2) Postsynaptic inhibition of the tract cells of the spinothalamic pathway exerted by inhibitory interneurons which are activated by A-α and β fibers. Disturbances of the inhibitory interneurons may result in paroxysmal pain triggered by inocuous stimuli. (3) Postsynaptic inhibition of the tract cells exerted by activation of descending pathways originating in the brain stem (PAG, NRM) which are probably serotoninergic. (4) Substantial increase in $(K)_e$ (above 6 mmol/1), induced by neuronal activity, can decrease efficacy of impulse transmission at the segmental level of the spinal

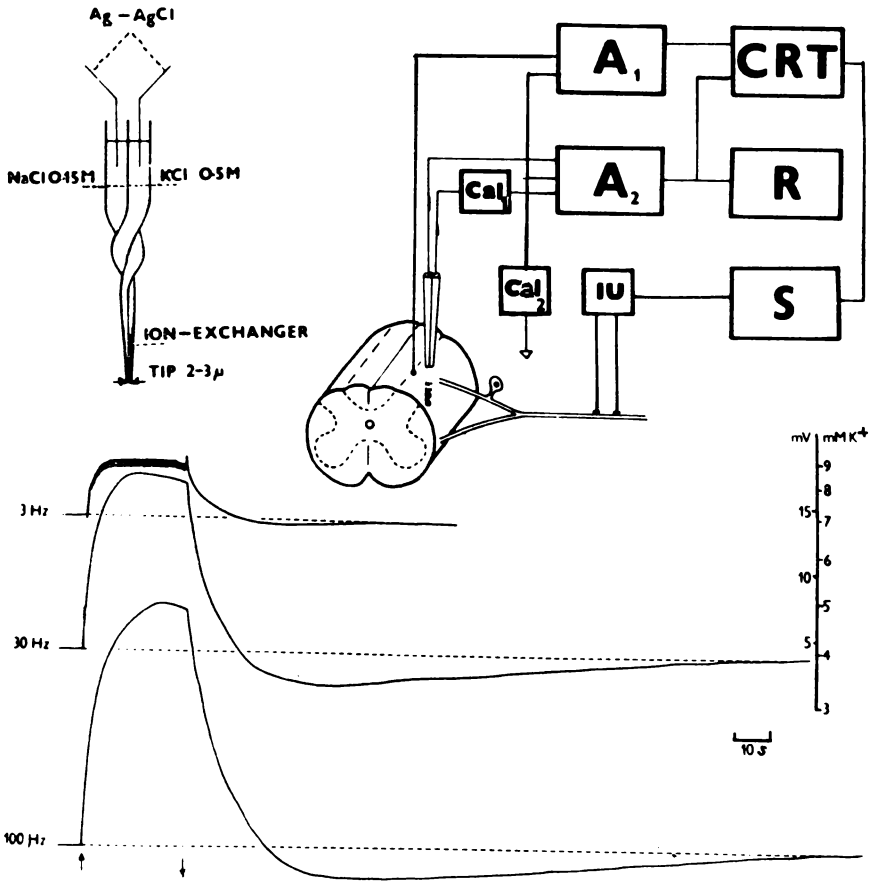

Fig. 4. Changes in the activity of potassium ions in the spinal cord of the cat induced by afferent stimulation. Measurements were performed with a double-barrelled potassium-sensitive microelectrode which is shown schematically in the left upper corner. The tip of one of the channels was filled with liquid potassium exchanger (Corning 477317) and the other channel served as reference electrode. The diagram in the right upper corner represents experimental arrangement for recording. The curves are original records of the changes in potassium activity in extracellular space in the intermediate nucleus of the spinal cord of the cat induced by stimulation of a mixed peripheral nerve at the frequency of 3 Hz, 30 Hz and 100 Hz. Calibration curve on the right side indicates potential shifts in mV produced by changes in potassium concentration in testing solution given in mmol/l.

cord. (5) Inhibition of neuronal pathways involved in pain perception by endogenous opiates (enkephalines and endorphins).

I realize that this is still a very simplified model of gating mechanism for pain perception, which only extends and modifies the original one proposed by Melzack and Wall (13), and that new data will modify it

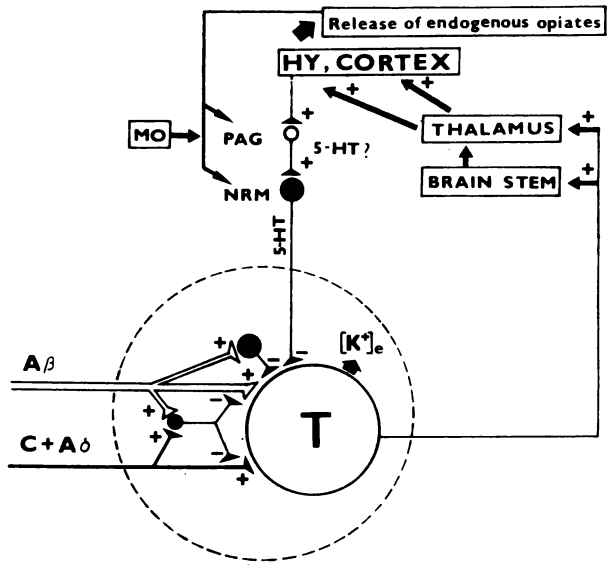

Fig. 5. Model of neuronal circuits which participate in control mechanisms of impulse transmission from the nociceptors. A-β (large-diameter afferent fibers) and *C* and A-δ (small diameter afferent fibers) activite tract cells (T) of the ascending pathways to the brain stem and to the thalamus and the interneurons, producing presynaptic inhibition. A-β fibers activate in addition the interneurons which exert a strong inhibitory action on the tract cells. Tonic inhibition on the T cells is exerted by serotoningergic (5-HP) descending pathway, originating in the brain stem — nucleus raphe magnus (NRM). Morphine (MO) and endogenous opietes interact with the opiate receptors in the cell membranes in the periaqueductal gray (PAG) and the nucleus raphe magnus (NRM). +, indicates excitatory; —, inhibitory action.

soon. Its only ambition is to find a better understanding between researchers who aim at finding more efficient means of suppressing pain that lost its physiological meaning and became a medical problem.

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