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Pain Research in Czechoslovakia

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This minireview is not intended to give a complete account about the contribution of Czechoslovak scientists to the present knowledge on pain and therapy. Rather, it should serve as the author's commentary in which he aims to express his personal view on the intellectual backgrounds which led many Czechoslovak physiologists and physicians to the present understanding that pain research needs a multidisciplinary approach of scientists from many clinical disciplines and basic sciences. This view was enthusiastically accepted at the symposium on Pain held at Issaquak (Washington, USA) in 1973. Due to the enormous energy of John J. Bonica, who organized this symposium, the International Association for the Study of Pain (IASP) was founded in 1974 and its main principles and goals were formulated. IASP has already organized six successful world congresses on pain in which the results of pain research and therapy were presented and immediately published. Local or regional chapters of IASP were established in many countries. In spite of several attempts it was not until 1987 that the Czechoslovak Pain Society was founded on the occasion of the 200th anniversary of the birth of the Czech physiologist J.E. Purkyně. At the beginning our Pain Society was a section of the Anaesthesiological Society and in 1989 it was recognized as an independent organization of the Czechoslovak Medical Society. It represents now 200 scientists and physicians. On the occasion of the Conference on Pain which was organized in 1989 during the council meeting of IASP in Prague, the Czechoslovak Pain Society was recognized as a Provisional Chapter of IASP. The merit for the activities leading to the establishment of a pain organization in Czechoslovakia has to be ascribed to two anaesthesiologists, J. Drábková and D. Miloschewsky, and a neurosurgeon, K. Šourek, who became its first president.

There have been several reasons for the fast spread of ideas in need of a multidisciplinary international cooperation in studying pain in the late sixties and early seventies. Firstly, the ideas on human rights were extended in the sense that people all over the world have the right to live not only without any restrictions of personal freedom but also without pain. Secondly, due to the wide spread of electrophysiological techniques, many laboratories were prepared to study neuronal pathways and mechanisms of impulse transmission activated by nociceptive stimulation in animal models. It was believed that if we understood neuronal mechanisms of nociception in animals it would be possible to use this knowledge for developing better techniques in the treatment of pain in the clinics (Zimmermann 1979). Thirdly, new concepts based on thoughtful examination of pain syndromes in

man were developed by psychologists (Melzack 1970) and were found useful by many clinicians in searching for new alternatives in the treatment of pain in patients. This started a new era of pain research in which new techniques for the study of nociception in animals were developed (see Vyklický 1983) and new, sometimes controversial, but always inspiring ideas were formulated. Many of them can be traced in the papers published in Pain, the official journal of IASP since 1974, or in the proceedings of the world congresses on pain.

In Czechoslovakia, alleviation of pain has traditionally represented a priority aim in medical praxis similarly as in many other countries. Pain has been considered a symptom which accompanies many diseases and therefore medical care has been primarily oriented towards the treatment of the cause of its origin. Only when this was not possible or an obvious reason for pain had not been detected, attempts were made to alleviate it by adequate means. In his book "Surgery of Pain" (1961) Arnold Jirásek described the attitudes of prominent Czech and Slovak physicians to the treatment of pain and presented indications for neurosurgical intervention. The book summarized contemporary knowledge on the physiology of pain at that time available, and presented a description of the main pain syndromes with vivid clarity. Jirásek's "Surgery of Pain" is apparently the first comprehensive book devoted exclusively to pain and can be considered a classic in Czech literature. Šourek's book "Surgery of Pain" (1981) published twenty years later encompasses all modern concepts of neuronal mechanisms of pain. The author carefully restricts indications for neurosurgical intervention in the treatment of chronic pain although he himself introduced several techniques of which mediolongitudinal chordotomy was recognized as highly efficient in relieving malignant pain (Šourek 1980).

Profound interest in surgical treatment of nonmalignant pain have been oriented to trigeminal neuralgia (Tic douloureux). Z. Kunc, a honorary member of IASP, performed over 250 operations in patients suffering from trigeminal neuralgia in which he adopted and further elaborated a technique of spinal trigeminal tractotomy, originally introduced by Sjöqvist (1938). His carefully documented results (1964) supported Olszewski's view (1950) that the first relay for impulse transmission from nociceptive afferent fibres in the trigeminal nerve is located in the caudal part of the nucleus tractus spinalis nervi trigemini.

Special credit with respect to the development of new methods in pain therapy has to be ascribed to many Czech and Slovak physicians and scientists in the rehabilitation and manual therapy who were inspired by the pioneering work of K. Lewit (1976). This neurologist well-known in our country developed efficient techniques for relieving pain in syndromes of vertebrogenic origin that represent frequent disorders with serious social consequences. Although the principles of the procedures are simple, their application to specific regions of the body is difficult to describe as to be fully understood and safely used in clinical practice. This is apparently the main reason why the majority of practical courses on rehabilitation of pain predominate over the relevant papers published (Lewit 1979). I do not hesitate to suggest that this field of clinical pain research and pain therapy merits international recognition.

Animal models for testing the analgesic effects of drugs have been developed and used. Some of them are original for their reliability and simplicity (Jezdinský 1982). The same applies to the technique for well defined application of radiant

heat as a nociceptive stimulus which was used in several studies on stress-induced analgesia (Jakoubek 1984).

Inspired by the findings and profound interests of E. Gutmann and his colleagues in the mechanisms of muscle atrophies of neurogenic origin (Gutmann and Vodička 1953, Gutmann 1963), Hník with his group developed animal models which enabled the study of reflex muscle atrophy induced by chronic peripheral nociceptive stimulation with the aim to understand better muscle atrophies which frequently accompany local pain in patients (Piťha 1937). Though it is obvious that reflex muscle atrophy differs from that produced by denervation, its mechanisms are still unknown and remain in the scope of experimental interest (Hník *et al.* 1977).

With the aim to understand visceral pain a prominent group of Slovak neuroscientists led by P. Duda significantly contributed to our knowledge of impulse transmission and supraspinal control of the neuronal pathways activated from visceral nociceptors (Pavlásek *et al.* 1977).

The gate theory of pain (Melzack and Wall 1965) greatly influenced thinking of many scientists all over the world. Undoubtedly the Czech translation of the Melzack's book "The Puzzle of Pain" (1978) contributed to the rapid spread of these new ideas on pain and nociception in Czechoslovakia.

The gate theory was scrutinized by neurophysiologists, further developed by new concepts formulated by psychologists and its validity was tested by clinicians who were inspired to develop alternative techniques for the treatment of pain syndromes in patients. At early stages of the new era of pain research, the experimental finding that selective stimulation of the unmyelinated C afferent fibres produces hyperpolarization of primary afferent fibre endings in the spinal cord and thus increases the efficacy of synaptic transmission (Mendell and Wall 1964) could not be confirmed by three independent groups of scientists who investigated the effects of selective stimulation of C afferents by using electrical stimuli or radiant heat (Franz and Iggo 1968, Zimmermann 1968, Vyklický *et al.* 1969). Although the reasons for this discrepancy have not been explained to full satisfaction, this fact seems of minor importance in respect to the basic ideas of the gate theory (Nathan 1976) because it was subsequently shown that impulse activity produced by nociceptive stimulation can be gated at several levels in the central nervous system (Fields and Basbaum 1979). In addition, Melzack and Wall (1965) already mentioned in their original paper that the gate mechanism for impulse transmission from nociceptors might be located postsynaptically.

Radiant heat, although a reliable source of nociceptive stimulation which can be precisely defined and localized, produces asynchronous activity which is not easy to detect while tracing neuronal pathways involved in pain sensation. The general belief of dentists that the only mode of sensation of pain which can be evoked by any kind of stimulation of the tooth pulp is pain, led researchers to assume that it might be an ideal afferent input which could be used for tracing neuronal pathways of nociception. An earlier study of Brookhart *et al.* (1953) indicated that the tooth pulp in the cat is exclusively innervated by Aδ fibres with a maximum impulse conduction velocity of 45 m/s. This was in agreement with the classical studies (Adrian 1931, Zotterman 1939) which demonstrated that only Aδ and unmyelinated C fibres, but not the fast conducting fibres Aβ, serve the sensation of pain.

It was found easy to stimulate the tooth pulp of the canine tooth in cat electrically both in acute and chronic preparations (Vyklický 1979).

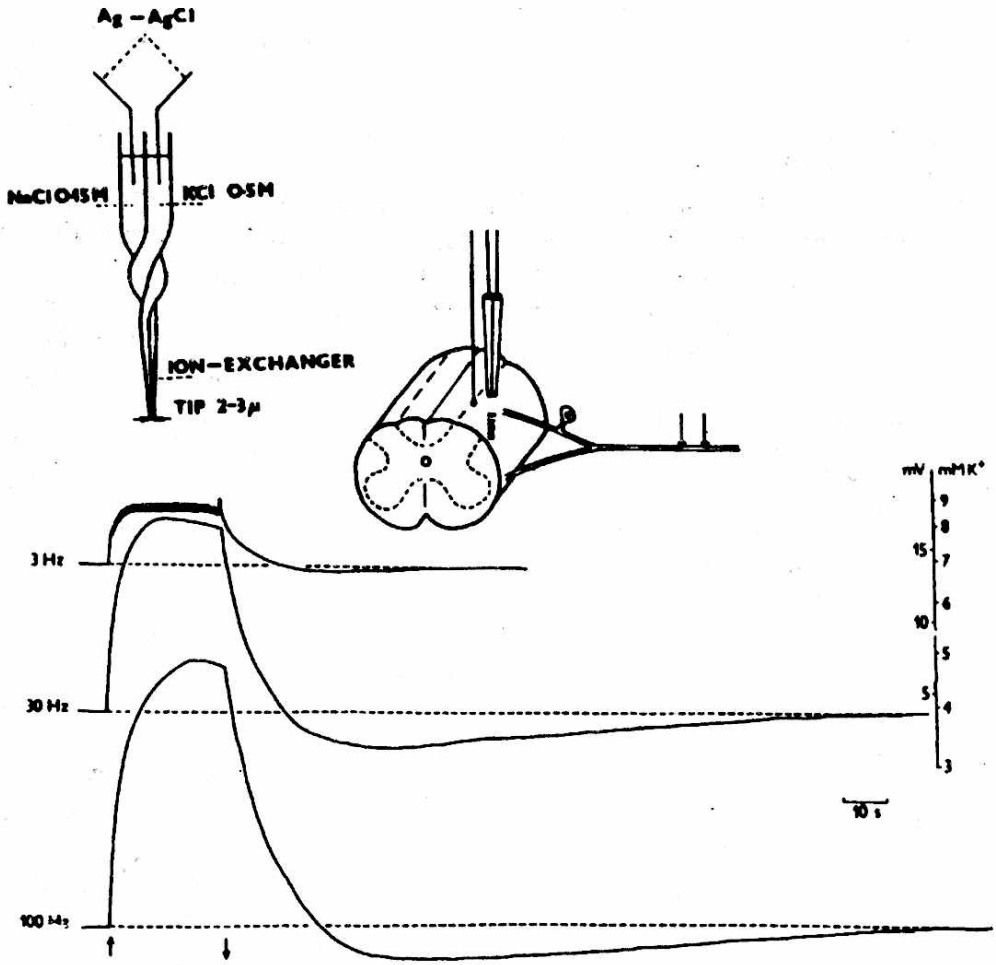

Fig. 1
Neuronal activity in the rostral part of the spinal trigeminal nucleus in the cat evoked by single electrical stimuli to the tooth pulp. A – Schematic arrangement for the application of electrical pulses to the canine tooth. B – Drawing of the medulla with schematic arrangement for recording neuronal activity. C and D – Field potential and unitary activity evoked by single electrical pulses applied to the tooth pulp.

While searching for the first relay of impulse transmission from the tooth pulp afferents in the trigeminal nucleus (Fig. 1), the first unexpected finding was that a large field potential was detected in pars oralis of the nucleus tractus spinalis nervi trigemini (Vyklický *et al.* 1970, Davies *et al.* 1971) and not in the pars caudalis as expected from the studies in which tractus spinalis nervi trigemini was transected to obtain relief from trigeminal neuralgia in patients (Sjöqvist 1938, Kunc 1964, 1970). In later studies, the projection of the tooth pulp afferents in the brain stem was further investigated (Keller and Vyklický 1982) and extended to the monkey (Tamarova *et al.* 1973). The findings were confirmed subsequently by histochemical techniques using horseradish peroxidase as a tracer (Ardvidsson and Gobel 1981, Tsuru *et al.* 1989). In the thalamus, impulse activity evoked by electrical stimulation

of the tooth pulp was detected both in the medial structures and in the nucleus ventroposteromedialis (Keller *et al.* 1974).

With respect to pain sensation, the findings of cortical projection of tooth pulp afferents (Vyklický *et al.* 1972, Andersson *et al.* 1973) were of special interest, because of a widely accepted view that pain does not have any cortical projection (Penfield and Boldrey 1937). The latter view was consistent with the findings of Hassler (1960) who did not observe any pain relief in patients suffering from intractable pain even when large areas of the cortex were removed bilaterally. On the contrary, after ablation of the cortex, pain was reported to be more widespread and excruciating. This finding, however, suggested that the cortex might play a role in the control of pain sensation. This view was supported by experiments which demonstrated that the transmission from the tooth pulp afferents is strongly inhibited after a train of electrical pulses applied to the cortical areas of the projection of tooth pulp afferents (Vyklický and Keller 1974).

An important question to be posed when studying pain in animal models is whether a change of the nociceptive reaction after surgical intervention in the central nervous system really reflects sensation of pain, because only man can communicate it verbally. In fact, the nociceptive reaction induced by tooth pulp stimulation in awake cats, which is characterized by jaw opening, differs very little from that which can be observed after intercollicular decerebration (Vyklický, not published). It was found very difficult to decide whether the spinal trigeminal tractotomy which was shown beneficial in patients suffering from trigeminal neuralgia (Sjöqvist 1938, Kunc 1964), alleviates pain evoked from the tooth pulp. A sophisticated procedure of evoking an avoidance reaction had to be elaborated in the cat to demonstrate that it did not have this effect (Vyklický *et al.* 1977). Later, similar results were obtained in the rat (Dallel *et al.* 1988) and it was confirmed in man that spinal trigeminal tractotomy does not prevent pain evoked from the tooth pulp (Young 1982).

Although tooth pulp was considered an ideal afferent input for tracing neuronal pathways of pain sensation, serious doubts were cast on the assumption that it is supplied exclusively by afferent fibres specific for this modality of sensation (Sessle 1979). It was demonstrated in man, that electrical stimuli applied to the tooth pulp well below the threshold for any sensation, can induce a silent period in EMG activity in masseter muscles during voluntary closing of the mouth (Matthews *et al.* 1976) . It has also been demonstrated that the tooth pulp is not only innervated by Aδ fibres but also by unmyelinated C fibres which represent an important afferent system for pain sensation (Närhi 1985, for review see Sessle 1987).

The gate theory inspired many scientists to search for the central mechanisms which could participate in controlling impulse transmission in neuronal pathways for nociception. Of special importance in this respect were the findings of Liebeskind and his colleagues (1974) who demonstrated that selective stimulation of the periaqueductal gray in the rat brain stem can induce analgesia without apparent changes in general behaviour or reflexes induced by tactile stimulation. Several medially located structures in the brain stem had already been previously identified as serotoninergic (Dahlström and Fuxe 1965) and other known to inhibit impulse transmission from high threshold primary afferents (Lundberg and Vyklický 1966). It was therefore suggested that the serotoninergic descending system in the brain stem plays an important role in controlling impulse transmission from peripheral

nociceptors at the segmental level (Fields and Basbaum 1979). This system is also very likely involved in stress-induced analgesia (Mayer and Watkins 1981, Jakoubek 1984, Jakoubek *et al.* 1987, Sumová and Jakoubek 1989).

Opioid receptor system has been analyzed in great detail and there is no doubt that it plays an important role in pain sensation (Kosterlitz and Paterson 1985, Herz and Teschenmacher 1971). The opioid receptors can be activated by opiates of exogenous origin, i.e. morphine and its synthetic derivates which represent drugs commonly used in controlling intractable pain. It has been suggested that activation of opioid receptors by endogenous ligands could also play a role in the analgesia induced by transcutaneous stimulation or acupuncture.

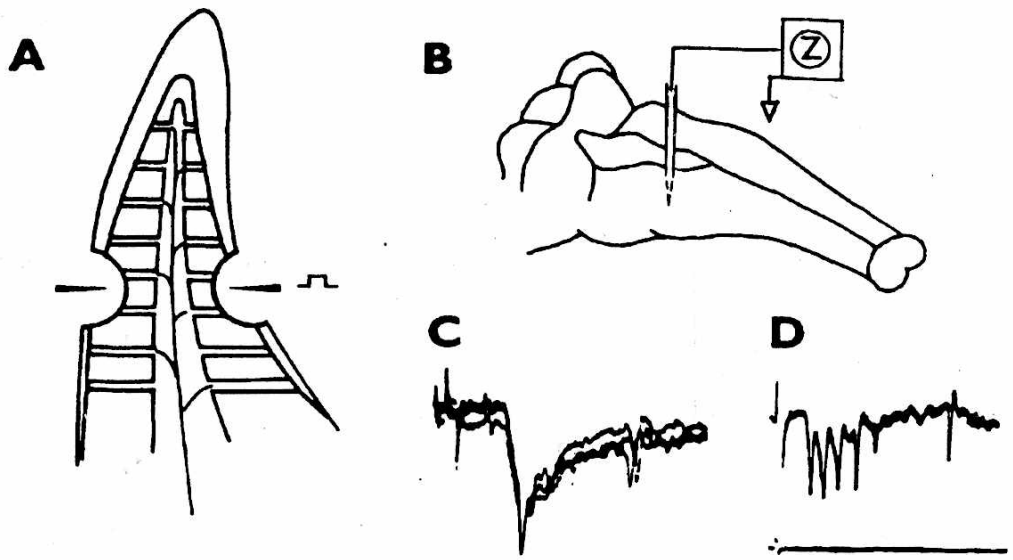

Fig. 2
Accumulation of potassium in the extracellular space at the segmental level of the spinal cord in the cat during tetanic stimulation of the posterior tibial nerve at the frequency indicated next to each record. Measurements were made with a liquid potassium-sensitive microelectrode (From Kříž *et al.* 1975).

In explaining some of the effects of transcutaneous stimulation in controlling pain it is, however, not necessary to assume that activation of the endogenous opioid system represents the only mechanism involved in analgesia. It was demonstrated that high-frequency stimulation of peripheral nerves leads to the accumulation of extracellular potassium at the segmental level of the spinal cord which can increase from its resting concentration of 3 mmol/l to 9 mmol/l (Fig. 2) (Kříž *et al.* 1974, 1975). Potassium is released mostly from secondary neurones during impulse activity and to a lesser extent from the primary afferents (Vyklický *et al.* 1976). Accumulated potassium can account for both the increase of excitability of secondary neurones resulting in facilitation of impulse transmission and the depolarization of primary afferents which accounts for the decreased synaptic efficacy due to presynaptic inhibition. It has been demonstrated that impulse transmission in the spinal cord of the frog is not attenuated until the concentration of extracellular potassium exceeds 6 mmol/l (Vyklický and Syková 1980). This may be at least one of the reasons for the frequent inadequacy of transcutaneous stimulation in the treatment of pain in

patients. The multiplicity of feedback mechanisms in the central nervous system is schematically depicted in Fig. 3.

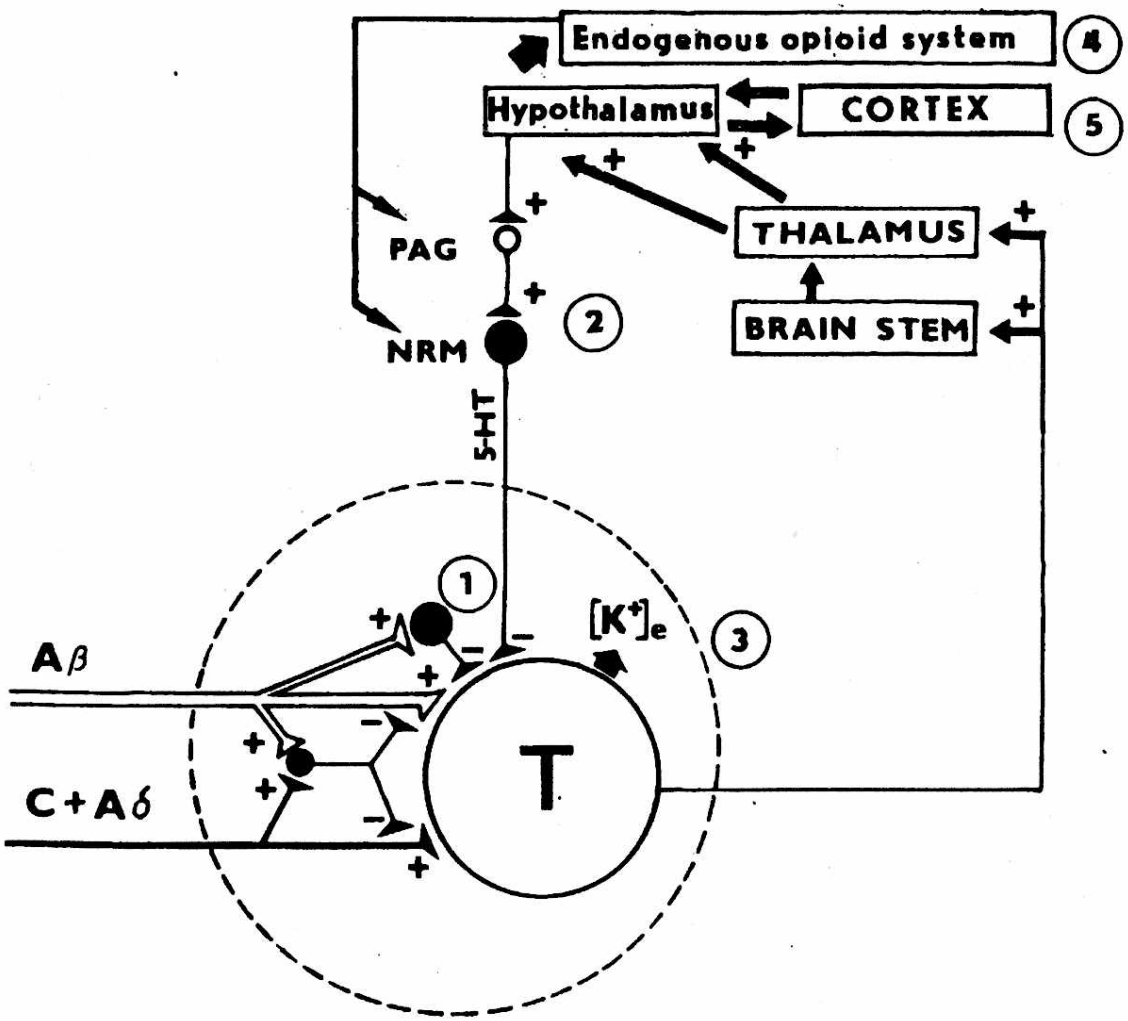

Fig. 3
Feedback mechanisms involved in the control of impulse transmission from primary afferent fibres or nociception. 1. Inhibitory neurones at the segmental level, 2. serotoninergic descending pathways, 3. potassium accumulation, 4. endogenous opioid system, 5. cortex.

Although one can agree with the view of Melzack (1988) and many of the members of IASP that the present knowledge about the treatment of pain makes it possible to ensure that everyone can live without pain, it has to be stated that cellular and molecular mechanisms of pain are still poorly understood and that much has to be done in order to treat pain both to the patient's and the physician's satisfaction. There is no doubt that the multidisciplinary approach to the investigation of pain at the national and international level will provide new knowledge which will lead to new strategies for more efficient control of chronic pain in patients.

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