CHEMOSENSITIVITY OF DORSAL ROOT FIBERS TO POTASSIUM IONS AND A HYPOTHESIS CONCERNING THE PERIPHERAL MECHANISM OF PAIN

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Potassium ions can excite dorsal root fibers, thereby evoking nociceptive reflexes. The threshold concentration for this effect, 20 mmoles/liter, is lower than that for the reflexogenic zones of the cardiac membranes and small intestine. The results are regarded as confirming the view that nociceptive responses are due to excitation, not of special nociceptive receptors, but of thin (nonmedullated) fibers directly.

The results of quantitative investigations of the chemosensitivity of receptive zones of the small intestine, hind limb, and cardiac membranes [1-6] led one of the authors (V. M. Kh.) to develop a new hypothesis concerning the peripheral mechanism of secondary (visceral, deep) pain [4]. Two of the assumptions of this hypothesis are fundamental. In contrast to the theory of "specificity" [16], of a "pattern of excitation" [15], and of "control at the input" [12], it is postulated that nociceptive stimuli do not excite special "pain" receptors but act directly on nonmedullated fibers. It is also assumed that nociceptive responses arise only if a stimulus excites a certain number of these fibers simultaneously, evoking synchronized discharges.

However, because of dispersion of conduction velocities, the synchronized volley arising in the fibers is desynchronized, even in the case of a functionally homogeneous group [8]. The longer the afferent pathway, the higher the degree of desynchronization. Consequently, the more distant the receptive zone from the spinal cord, the greater the threshold intensity of stimulation for the production of nociceptive reflexes (and in particular, the higher the concentration of chemical substances) [5]. The threshold concentration of potassium ions for production of nociceptive reflexes is 62.5-125 mmoles/liter for the receptive zone of the hind limb [6], about 40 mmoles/liter for the small intestine [1-3], and about 30 mmoles/liter for the cardiac membranes [5].

Results obtained by Calma and Wright [7], according to whom potassium ions, acting on the dorsal root of the spinal cord, evoke a pressor reflex in concentrations as low as 18 mmoles/liter, are of interest in connection with this hypothesis. The object of the present investigation was to verify this report and to determine whether potassium ions can in fact excite dorsal root fibers, and can do so in lower concentrations than the threshold for nociceptive reflexes from more distant zones of the spinal cord.

EXPERIMENTAL METHOD

In experiments on cats anesthetized with urethane (1.5-2 g/kg) the spinal cord (L_4-S_1) was exposed and the dorsal root L_7 divided and drawn out by means of a ligature through a chamber (Fig. 1) so that the divided end of the root remained outside the chamber. The holes in the chamber were sealed hermetically with petroleum jelly. The spinal cord was irrigated with mineral oil.

The action of KCl solutions whose concentration was doubled for each stimulation (from 15.6 to 500 mmoles/liter) was investigated in 12 experiments. The KCl acted only on that part of the root which was inside the chamber. The test substance was rinsed out by passing Ringer – Locke solution repeatedly

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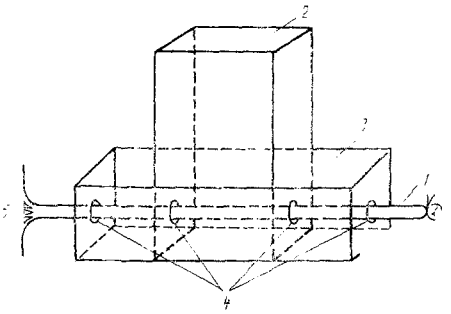

Fig. 1. Scheme showing manipulation of dorsal root: 1) dorsal root; 2) inner part of chamber containing KCl solution; 3) petroleum jelly seals; 4) holes for dorsal root; 5) spinal cord.

through the chamber (37°). To obtain a more accurate estimate of the special concentration, the action of KCl was investigated in a further 8 animals in concentrations of 15.6, 23.4, and 31.2 mmoles/liter. The degree of stimulant action was estimated from the change in arterial pressure, recorded in the carotid artery.

EXPERIMENTAL RESULTS AND DISCUSSION

As in the experiments of Calma and Wright [7], and also in those of Laget and Lundberg [10], potassium ions acting on dorsal root fibers evoked exclusively pressor reflexes (Fig. 2A). Reflex excitation of respiration occurred at the same time. These reflexes persisted relatively unchanged during the action of KCl but disappeared when it was replaced with Ringer – Locke solution.

With an increase in the KCl concentration the pressor reflexes increased in degree but became less stable, dying away while the KCl was still acting. Nevertheless, repeated rinsing of the dorsal root was necessary to abolish them.

The curve of concentration against amplitude of reflexes in this experiment (Fig. 2B) and the curve of mean amplitudes of the reflexes (Fig. 3) lay within the concentration range 15.6-500 mmoles/liter and

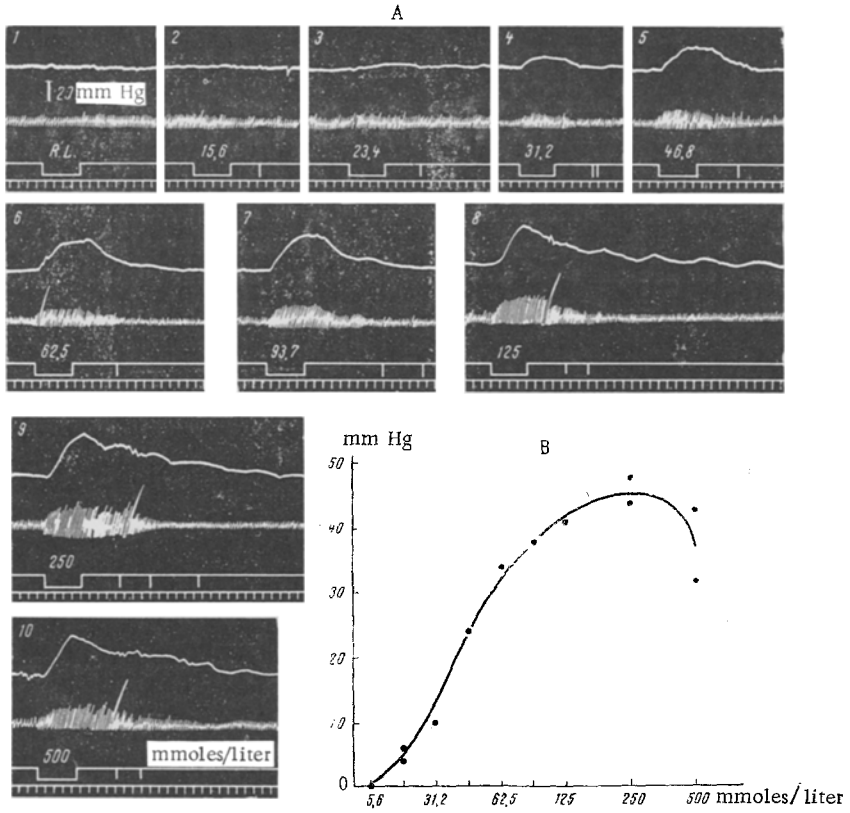

Fig. 2. Reflexes affecting arterial pressure and respiration during stimulation of dorsal root L_7 with KCl solution (A) and curve of concentration against amplitude of pressor reflexes (B). In A, from top to bottom: arterial pressure, respiration, marker of stimulation (20 sec) and rinsing, time marker (5 sec). Numbers above marker of stimulation denote KCl concentration (in mmoles/liter). Zero line coincides with marker of stimulation. In B: ordinate, amplitude of reflexes (in mm Hg); abscissa, KCl concentration (in mmoles/liter).

TABLE 1. KCl Concentrations (mmoles) Evoking Threshold Pressor Nociceptive Reflexes, Threshold Pseudoaffective Response, and Threshold Sensation of Pain in Man

Reflexogenic zone	Test object	Character of responses	KCl concentration (in mmoles/liter)	Literature citation
Dorsal root	Cats under urethane anesthesia	Pressor reflex	20	Present investigation
Cardiac membranes	Vagotomized cats under urethane anesthesia	The same	31.2	[5]
Small intestine	Cats under urethane anesthesia	" "	31.2-62.5	[2, 4]
Mesenteric nerves	The same	" "	31.2-62.5	[2, 4]
Distal part of hind limb	" "	" "	62.6-125	[6]
Proximal part of hind limb	Cats under barbiturate anesthesia	Pseudoaffective response	47	[3]
Arteries of various organs	Dogs under chloralose anesthesia	The same	125-250	[9]
Skin of forearm	Man	Sensation of pain	31.8-45.2	[1]
The same	The same	The same	32	[14]

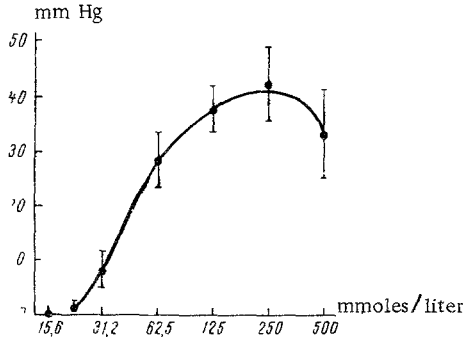

Fig. 3. Relationship between amplitude of pressor reflexes and KCl concentration (mean results of 12 experiments). Ordinate, amplitude of reflexes (in mm Hg); abscissa, KCl concentration (in mmoles/liter). Vertical lines denote twice the mean error of the mean.

were S-shaped. This character of the curve suggests that pressor reflexes are produced through excitation. not of receptors, but of afferent fibers directly. The corresponding curves for the receptive zones of the hind limb [6], small intestine [1], and cardiac membranes [5] have two limbs, the first due to excitation of receptors and the second to excitation of afferent fibers directly [2, 4]. In the dorsal root, the first limb of the curve is absent, just as it is when KCl is injected into the blood vessels of the mesenteric nerves [2, 4].

In 11 of 20 experiments threshold reflexes (mean amplitude 3 mm Hg) developed when the KCl concentration was 23.4 mmoles/liter, and in 6 experiments the threshold concentration was between 23.4 and 31.2 mmoles/liter. This is higher than the threshold concentration of 18 mmoles/liter found by Calma and Wright [7]. However, they do not state the number of experiments for which the concentration was determined. In two of the present experiments a concentration of 15.6 mmoles/liter was threshold. In five experiments of those included in a group in which the threshold concentration was 23.4 mmoles/liter, the reflexes were equal to or higher than 5 mm Hg in amplitude, while in one of them the threshold reflex attained 12 mm Hg, i.e., in these five experiments the true threshold concentration was between 15.6 and 23.4 mmoles/liter. It can thus be accepted that the KCl concentration adequate to produce threshold pressor reflexes when acting on the dorsal root in most experiments was 20 mmoles/liter.

The possibility cannot be ruled out, in principle, that receptors sensitive to potassium ions may be present in the dorsal root. However, the sensitivity of tissue receptors to potassium ions is higher than was discovered during their action on the dorsal root. During perfusion of organs with Ringer – Locke solution threshold pressor reflexes from tissue receptors excited by potassium ions are produced at a concentration of 7–8 mmoles/liter [14], whereas during perfusion with blood, the excess of these ions need be only 2–4 mmoles/liter [1, 4]. Consequently, the threshold of excitation of the dorsal root zone by potassium ions is 2.5–3 times higher than the threshold of excitation of tissue receptors. This suggests that pressor reflexes evoked by potassium ions are due to direct excitation of the dorsal root fibers, and are a response to what can be regarded as nociceptive stimulation.

The results given in Table 1 show that a gradient of threshold nociceptive concentrations of potassium ions exists, rising with increasing distance of the reflexogenic zone from the spinal cord. The existance of this gradient can be regarded as indirect confirmation of the hypothesis that the transmission of information concerning nociceptive stimulation takes place through impulses grouped into synchronized volleys.

The fact that a sensation of pain arises from the skin of the human forearm in the presence of a lower concentration of potassium ions [11, 14] than in experiments in which these ions are injected into the blood vessels of the hind limb in animals [6, 9, 13] is probably explained by the fact that their reception is not influenced by anesthesia.

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