THE BRAIN STEM AND THE VERY LATE REFLEX RESPONSE OF VASOCONSTRICTOR NEURONS TO IMPULSES OF SOMATIC A-AFFERENTS

Yu. B. Gailans, E. V. Lukoshkova, and V. M. Khayutin

UDC 612.826.:612.833

Single stimulation of A-fibers of the tibial nerve evoked not only a late response – a discharge of the latent period 60-140 msec – in the renal nerve of unanesthetized decerebrate cats, but also a very late response (VLR), with a latent period of about 0.35 sec. This response was easily elicited in nearly all experiments on "mesencephalic" animals, but after division of the brain stem at different levels of the pons, including the region of the pontobulbar junction and the most rostral portions of the medulla, it was discovered in only 1 of 18 animals. After division of the brain stem rather more caudally (in "bulbar" animals) VLR was found in 10 of 11 animals. In the region of the pontobulbar junction there are thus structures which tonically inhibit the activity of the system generating the VLR. It is shown that the activity of this system is potentiated by two types of summation processes: Some taking place during long (seconds) and others taking place during short (milliseconds) time intervals.

KEY WORDS: decerebration; somatosympathetic responses; arterial blood pressure reflexes.

Besides early and late responses of sympathetic neurons [8, 11, 14], the A-afferent volley of hind-limb cutaneous nerves can also evoke another response of these neurons, known as the "very late response" (VLR) [10, 13]. This name is given to the discharge because of its extremely long latent period – of the order of 0.3 sec. So far this response has been found only in cats with an intact brain (and with divided vagus, aortic, and carotid sinus nerves), only in preganglionic nerves, and only under extremely superficial general anesthesia. Even a very slight increase in the depths of anesthesia suppressed the VLR. After division of the brain stem at the middle of the pons or above, the VLR disappeared. This suggested that the reflex pathway of VLR runs rostrally to the pons, and the arc of this responce can be called "suprapontine" [13].

In animals with an intact brain, depending on whether anesthetized or not, impulses in spinal A-afferents raise or lower the arterial blood pressure (BP) [7, 9, 12]. The particularly high sensitivity of the neuronal system generating the VLR to general anesthesia suggests that anesthesia alters the character of reflex responses of BP because it suppresses this system. In that case, the active or inactive state of the system can determine whether impulses in A-afferents give rise to pressor or depressor reflexes.

In anesthetized "mesencephalic" or "bulbar" cats the flow of impulses in $A\beta$-, $A\delta_1$-, and $A\delta_2$-afferents (conduction velocity 15-22 m/sec) of the tibial nerve (TN) raises BP [1]. However, the same flow (and often a more intensive flow including impulses in $A\delta_3$-afferents) lowers BP in cats decerebrated so that the medulla preserves its connections with the caudal formations of the pons [2].

If the suggestion that VLR play a decisive role in the mechanism of pressor reflexes is correct, it can be expected that: 1) this response will appear in "mesencephalic" animals; 2) it will be depressed if connections are preserved between the medulla and pons; 3) rupture of these connections will restore the mechanism of VLR. The experiments described below confirm all three suggestions and themselves provide a basis for the further suggestion that a vital condition for the occurrence of hypertensive reflexes is an active state of the system generating VLR of vasoconstrictor neurons.

Laboratory of Biophysics and Pathophysiology of the Circulation, Institute of General Pathology and Pathological Physiology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii Meditsiny, Vol. 88, No. 10, pp. 390-393, October, 1979. Original article submitted June 7, 1978.

0007-4888/79/8810-1100$07.50

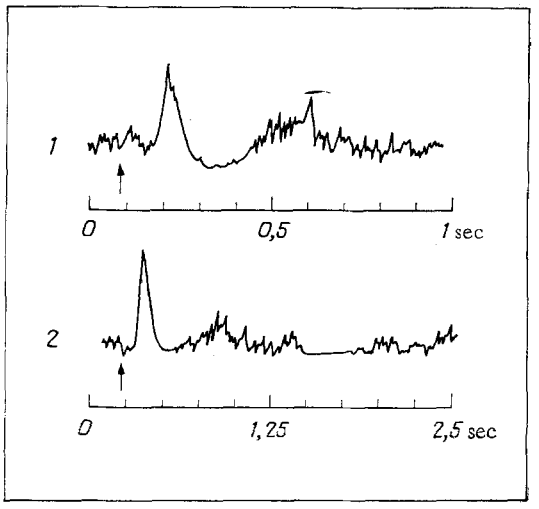

Fig. 1

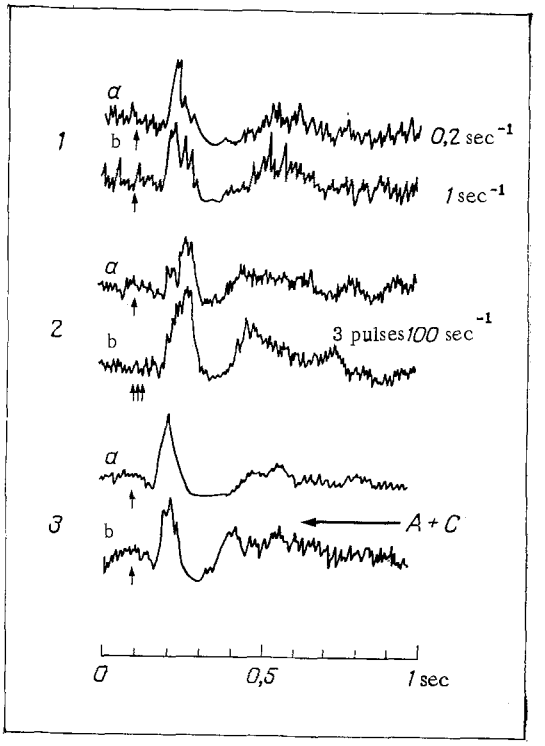

Fig. 2

Fig. 1. Late and very late reflex A-responses in "bulbar" (1) and "mesencephalic" (2) cats. Averaging of 20 responses to stimulation of tibial nerve by single pulses (3 V, 0.1 msec, interval between stimuli 5 sec). Arrows show times of application of stimuli.

Fig. 2. Increase in amplitude of very late response to stimulation of A-fibers of tibial nerve (3 V, 0.1 msec) on shortening interval between single stimuli (1b), during stimulation with short volleys of stimuli (2b), and after tetanic stimulation of A +C-afferents of tibial nerve (3b). 1, 2) "Bulbar" cats, 3) "mesencephalic" cat. Traces marked *a* are control. Interval between stimuli (or volleys of stimuli) in all traces except 1b was 5 sec. Arrows mark times of application of stimuli.

EXPERIMENTAL METHOD

Since the details of the method were described previously [1-4], all that will be said here is that the experiments were carried out on ananesthetized decerebrate curarized, artificially ventilated cats. Decerebration was carried out under ether anesthesia by coagulation of brain tissues with a high-frequency current. The brain stem of 12 cats was divided in a plane passing through the mammillary bodies and immediately anteriorly to the corpora quadrigemina ("mesencephalic" animals); in 18 cats the brain stem was divided in various parts of the pons and also in the region of the pontobulbar junction and the most rostral portions of the medulla ("pontine" animals); in 11 cats it was divided a little caudally to this region ("bulbar" animals). The level and completeness of division of the brain stem in each experiment were verified in brain preparations fixed with formalin.

Responses were recorded in the left renal nerve. To excite A-fibers of the left TN it was stimulated electrically with pulses 0.1 msec in duration and not over 3 V in amplitude, sufficient to excite nearly all A-fibers of TN but below the threshold of excitation of its C-fibers [5, 8]. Stimuli 1 msec in duration and 15 V in amplitude were used to excite the A +C-fibers of TN. The reflex responses were averaged by an ATAS-201 apparatus, to the input of which signals were led from the UBP1-02 amplifier through a bridge circuit converting bipolar signals into monopolar. Usually responses to 20 consecutive stimuli were averaged. The pressure in the right femoral artery (contralateral to the stimulated TN), verified by a mercury manometer, was between 110 and 160 mm Hg.

EXPERIMENTAL RESULTS

In the renal nerve of decerebrate animals the inhibitory component of the late response may be interrupted by the appearance of yet another response. Its latent period for the two cases recorded in Fig. 1 was

about 0.35 sec. The averaged amplitude of this response was less than the mean amplitude of the late response, but its duration was much longer. The minimal strength of stimulation of TN required to cause the appearance of this very long latency response was 0.5-0.7 V. Stimuli of this amplitude excite both $A\beta$- and $A\delta_1$-afferents and $A\delta_2$-afferents of TN [5]. Admittedly, in most experiments this response developed only when the amplitude of the single stimuli exceeded 1-1.5 V, i.e., when it was sufficient to excite $A\delta_3$-afferents also [5]. The discharge in the renal (postganglionic) nerve, interrupting the inhibitory component of the late A-response, thus appeared after approximately the same latent period and to stimuli of the same amplitude as in preganglionic nerves [13]. Consequently, this was the same response in both cases and, just as in the paper by Sato [13], it must be called "very late." Since the renal nerve consists almost entirely of vasoconstrictor fibers [5, 8] it is clear that the VLR is generated by vasoconstrictor neurons (this does not rule out the possibility that the same response may also be generated by other sympathetic neurons).

The reflex pathway of VLR is not suprapontine: This response appeared in 8 of 11 "bulbar" cats (Fig. 1, 1) and, consequently, preservation of connections of the spinal cord with the greater part of the medulla was sufficient for its generation. The very late response was found also in nine of the 12 "mesencephalic" animals (Fig. 1, 2), but among the "pontine" animals it could be detected in only one of 18.

In the experiments in which VLR was weak, it could be intensified by shortening the intervals between single stimuli to 2 or 1 sec (Fig. 2: 1), or by stimulating A-afferents with 2 or 3 stimuli at intervals of 2.5-50 msec (Fig. 2: 2). Short (10-15 sec) tetanic stimulation of A+C-afferents of TN, which increased the sensitivity of the dorsal horn neurons to the volley of A-afferents of the same nerve for a few minutes, facilitates the appearance of the late response [6]. This procedure also facilitated the appearance of the very late A-response (Fig. 2: 3). The methods of increasing the effectiveness of action of volleys of A-afferents mentioned above (both individually and in various combinations) enabled a VLR to be discovered in three "mesencephalic" and in two of the three "bulbar" animals, in which it could not be evoked by single stimuli separated by intervals of 5 sec. A VLR was thus discovered in all the "mesencephalic" cats and in 10 of 11 "bulbar cats. Its latent period was 0.36 ± 0.08 sec (mean value $\pm$dispersion) for the former and 0.33 ± 0.05 sec for the latter. These methods of detection of VLR were effective in only four of the 13 experiments on "pontine" animals in which these methods were used and in which it was not induced by single stimuli (repetition period 5 sec).

Hence, as was expected, preparations of the caudal regions of the pons and even the most rostral portions of the medulla prevents the appearance of the VLR. It can tentatively be suggested that the absence of the VLR in most "pontine" animals was due either to particularly intensive inhibition of preganglionic neurons, developing during the appearance of the late response preceding the VLR, or to descending tonic inhibition of the interneuronal system generating the VLR. Formations located in the region of the pontobulbar junction and in the rostral portions of the medulla are the source of these influences.

The activity of the system generating the VLR is potentiated by summation processes taking place over long (seconds) and short (milliseconds) time intervals. The summation process of the first kind is manifested as a marked decrease in the latent period of the VLR on shortening of the intervals between single stimuli (or short volleys of stimuli): During stimulation with a frequency of 1 Hz the latent period of VLR may be reduced to 0.2 sec. Probably more frequent stimulation would increase the excitability of the interneuronal systems generating the VLR, and so increase the probability of excitation of preganglionic neurons which discharge after the shortest latent period. The minimal latent period of discharge of single preganglionic neurons corresponding to the VLR is known to be 0.2 sec, and the maximal latent period 0.5 sec [10].

The summation process of the second type augments the VLR in the case of double or triple repetition of the A-afferent volley at intervals of 2.5-50 msec. These secondary volleys ought to excite the interneuronal system generating the VLR more intensively, as a result of which the number of impulses in this system capable of overcoming the inhibition to which the preganglionic neurons are subjected during the formation of the late response is evidently increased, with a corresponding increase in the number of preganglionic neurons generating the very late discharge. The essential point is that because of the summation process of the second type a VLR can be evoked by a short volley of stimuli whose amplitude is sufficient to excite only a small proportion of $A\delta_2$-afferents (0.3 V). The necessity for excitation of $A\delta_3$-afferents before a VLR can appear in response to single stimulation of VLR is also determined by a summation process of the second type: In this case, the potentiates spatial summation and increases the time taken for the afferent volley to reach the CNS.

It remains to be added that the particularly long duration makes the VLR functionally the most important component of somatosympathetic reflex discharges, i.e., the principal discharge responsible for hypertensive reactions of the vasoconstrictor system to impulses in somatic A-afferents [1-3].

LITERATURE CITED

1. Yu. B. Gailans, E. V. Lukoshkova, and V. M. Khayutin, Byull. Éksp. Biol. Med., No. 10, 393 (1977).
2. Yu. B. Gailans, E. V. Lukoshkova, and V. M. Khayutin, Byull. Éksp. Biol. Med., No. 11, 519 (1978).
3. Yu. B. Gailans, E. V. Lukoshkova, and V. M. Khayutin, Byull. Éksp. Biol. Med., No. 2, 114 (1979).
4. Yu. N. Grishanov, I. K. Evstifeev, and V. M. Khayutin, Byull. Éksp. Biol. Med., No. 3, 378 (1978).
5. E. V. Lukoshkova, in: Problems in Space Biology [in Russian], Vol. 31, Moscow (1975), pp. 135-157.
6. E. V. Lukoshkova and G. Pavlik, Pflüg. Arch. Ges. Physiol., 336, 134 (1972).
7. V. M. Khayutin, in: Current Problems in the Physiology and Pathology of the Circulation [in Russian], Moscow (1961), pp. 193-232.
8. V. M. Khayutin, R. S. Sonina, and E. V. Lukoshkova, The Central Organization of Vasomotor Control [in Russian], Moscow (1977).
9. J. Colle and J. Gybels, Arch. Int. Physiol. Biochem., 65, 547 (1957).
10. A. Kaufman and K. Koizumi, in: Research in Physiology, Bologna (1971), pp. 469-481.
11. K. Koizumi and C. McC. Brooks, Ergebn. Physiol., 67, 1 (1972).
12. H. McLennan, Pflüg. Arch. Ges. Physiol., 273, 604 (1961).
13. A. Sato, Pflüg. Arch. Ges. Physiol., 332, 117 (1972).
14. A. Sato and R. F. Schmidt, Physiol. Rev., 53, 916 (1973).

DIGESTION OF MILK PROTEINS AND LYSOSOMAL PROTEINASES OF THE ILEAL MUCOSA OF YOUNG RATS

V. R. Nikolaevskaya and M. P. Chernikov

UDC 612.664.7:612.398.3

To study whether lysosomal proteinases of the ileal mucosa can participate in intraluminal digestion, the proteolytic activity of lysosomal and pancreatic proteinases was determined both in the chyme and in a homogenate of ileal and jejunal tissues from rats aged 12 and 30 days. In the period of milk feeding the proteolytic activity of acid (lysosomal) proteinases was shown to be three times higher in the ileum than in the jejunum, and this was shown to be true both for the mucosa and for the contents of these parts of the small intestine. In rats which had changed over to a definitive diet, acid proteinase activity in the jejunum and ileum was almost unchanged both in the mucosa and in the contents. The results are evidence that pancreatic proteinases adsorbed from the chyme of the small intestine can participate in contact digestion.

KEY WORDS: early postnatal period; lysosomes; acid proteinases; milk proteins; pancreatic proteinases.

Data have recently been published to show that giant lysosomes are located in the brush border of the enterocytes in the distal portion of the small intestine in the early postnatal period of development in rats. The change from milk to definitive feeding is accompanied by disappearance of these lysosomes. It has been suggested that lysosomal enzymes participate in intracellular digestion during the period of milk feeding [6, 7].

The problem of the mechanisms lying at the basis of the high efficiency of utilization of milk proteins at an early age has not yet been solved. It is claimed that some milk proteins during this period can be absorbed in the unhydrolyzed state [9]. There is also evidence of the alimentary specificity of milk proteins, which determines the high efficiency of their utilization [1]. Some workers have noticed that the digestive system in the period of milk feeding is immature [7, 8], although the opposite views have also been expressed, namely that at an early age the level of development of the proteolytic system of digestion is relatively high [10].

Institute of Nutrition, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. N. Orekhovich.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 10, pp. 393-395, October, 1979. Original article submitted May 4, 1978.

0007-4888/79/8810-1103$07.50