EXPERIMENTAL STUDY OF THE EFFECT OF CAPTOPRIL ON NOCICEPTIVE REACTIONS

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Captopril (SQ 14.225) is an antihypertensive agent whose mechanism of action is linked with selective inhibition of the enzyme dipeptidyl-carboxypeptidase (EC 3.4.15.1), also known as "kinase II" and "angiotensin I-converting enzyme" (ACE) [11]. ACE reduces angiotensin II formation and delays bradykinin inactivation. Data obtained in recent years have shown that ACE also participates in metabolism of those enkephalins [13, 15] that possess analgesic activity [13, 15]. However, data in the literature on the effect of captopril on nociceptive reactions and on the pharmocologic effect of enkephalins are contradictory [2, 7, 8, 13].

In connection with the foregoing facts it was decided to study the effect of captopril on nociceptive reactions to various kinds of nociceptive stimulation and to conduct a pharmacologic analysis.

EXPERIMENTAL METHOD

The effect of captopril on nociceptive reactions to chemical and thermal stimulation was studied in male mice weighing 20-22 g. The action of the drug was evaluated relative to its ability to change the number of "contortions" induced by intraperitoneal injection of 0.025 ml of 1% acetic acid solution [3] and to alter the threshold of nociceptive sensitivity (TNS) by the use of hot plate (56.5°C) [9] and thermal stimulation of the tail (with the Hugo Sachs Elektronik analgesimeter, West Germany) [4] methods.

In all the experiments captopril was injected subcutaneously in doses of 0.1, 0.5, 1, 5, 10, and 25 mg/kg body weight 30 min before nociceptive stimulation. The action of each dose was studied in 8-10 mice. Animals of the control groups received isotonic NaCl solution injected in the same volume and by the same method as captopril.

In preliminary experiments on mice by the revolving rod methods [6] it was shown that captopril, in a dose of 25 mg/kg, does not affect skeletal muscle tone or movement coordination of the animal. Thus the effect of these factors on evaluation of the intensity of the nociceptive reactions could be ruled out.

The effect of captopril (in concentrations of 10^{-9} to 10^{-4} g/ml) on contractions of segments of the isolated ileum from guinea pigs of both sexes weighing 250-400 g, induced by electrical stimulation (square pulses, 0.1 Hz, 2-4 msec, 20-60 V) was studied. Contractions of the ileum, kept in a constant temperature bath (37°C) with a volume of 20 ml, through which Tyrode solution was passed at a constant flow rate (1 ml/min), were recorded under isometric

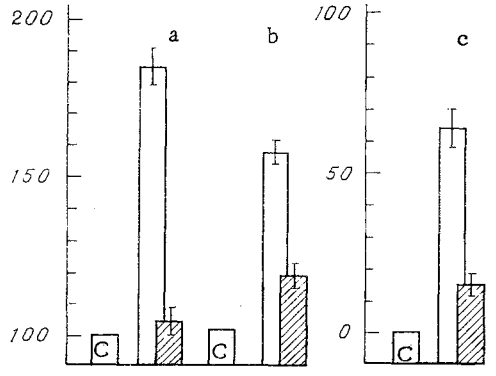

Fig. 1. Effect of naloxone (2.5 mg/kg, subcutaneously) on analgesic effect of captopril (25 mg/kg, subcutaneously) in mice during thermal (a, b) and chemical (c) nociceptive stimulation. Vertical axis — change (in percent) in TNS (a, b) and reduction (in percent) of number of "contortions" (c). C) Control. Shaded columns denote combined injection of captopril and naloxone.

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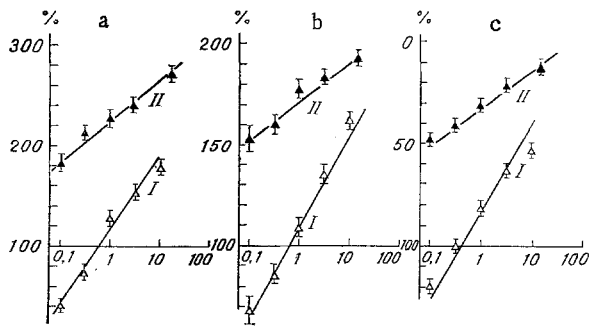

Fig. 2

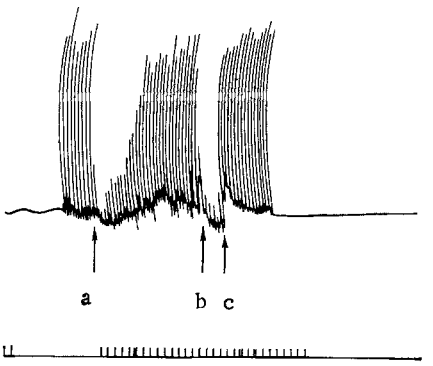

Fig. 3

Fig. 2. Effect of captopril on TNS of mice when placed on a hot plate (a) and in response to thermal stimulation of the tail (b), and also on number of "contortions" induced by intraperitoneal injections of acetic acid (c). Abscissa, dose of captopril (in mg/kg); ordinate, change in TNS and reduction in number of "contortions" (in %); I) captopril; II) captopril preceded by injection of cellulose sulfate (100 mg/kg, intravenously).

Fig. 3. Inhibition by captopril of contractions of isolated segments of guinea pig ileum induced by electrical stimulation, and its abolition by naloxone. Arrows indicate addition of drug to vessel containing organ: a) captopril (10^{-4} g/ml); b) the same; c) naloxone (10^{-6} g/ml). Time marker 60 sec.

conditions on an automatic writer (Unirecord, from Ugo Basile, Italy). Captopril and naloxone (10^{-6} g/ml), dissolved in Tyrode solution, were added directly to the vessel containing the organ. The action of each concentration of the drugs was studied on 5 or 6 segments of ileum.

The numerical results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

Depending on the dose, captopril had different effects on models of nociceptive reactions induced in mice by acetic acid and thermal stimulation. When injected in doses of 0.1 and 0.5 mg/kg it increased the number of "contortions" induced by acetic acid, but lowered TNS for thermal nociceptive stimulation (Figs. 1 and 2), i.e., it had a hyperalgesic action. Increasing the dose of captopril to 1, 5, 10, and 25 mg/kg led to a dose-dependent increase in TNS and a decrease in the number of "contortions," i.e., the analgesic effect of the drug was exhibited (Fig. 1).

Since the hyperalgesia observed in response to injection of small doses of captopril may be due to accumulation of endogenous kinins, as a result of disturbance of their inactivation, and the analgesic effect may be due to inhibition of enkephalin inactivation, two series of experiments were carried out to study the role of these mechanisms in the action of captopril. In one series of experiments, using cellulose sulfate (100 mg/kg intravenously 2 h before the experiment) as activator of kininogenesis, the animals were dekininized [1, 12]. In the other series of experiments, in which naloxone (2.5 mg/kg subcutaneously, 30 min before the experiment) was used, the possibility that endogenous enkephalins participate in the analgesic effect of captopril was studied.

Experiments on dekininized mice showed that under these conditions captopril, in both small and large doses and with all types of nociceptive stimulation, gave only an analgesic effect; this effect, moreover, was more marked than in animals with a normal kininogen level (Fig. 2). Blocking the kinin component thus facilitates manifestation of the analgesic effect of captopril. Meanwhile the opiate antagonist naloxone substantially weakened the analgesic effect of captopril (Fig. 1). This is evidence that the analgesia induced by it is linked with increased activity of the endogenous antinociceptive system (enkephalins, etc.).

In experiments on segments of the guinea pig ileum captopril, starting with a concentration of 10^{-6} g/ml, caused a dose-dependent reduction of the amplitude of contraction arising in response to electrical stimulation. In concentrations of between $5 \cdot 10^{-5}$ and 10^{-4}

g/ml it reduced their amplitude by 90-100%. Spontaneous recovery of the response of the ileum to stimulation developed gradually over a period of 5-10 min. Naloxone completely abolished the inhibitory action of captopril (Fig. 3).

Pharmacologic analysis of the action of captopril thus showed that its hyperalgesic action (in small doses) against the background of nociceptive stimulation depends on accumulation of endogenous kinins, whose metabolism is inhibited by captopril, whereas the analgesic effect depends on elevation of the endogenous enkephalin level. This hypothesis is supported by the results of experiments both on dekininized animals and with naloxone, which abolished the effects of captopril on the isolated guinea pig ileum and in whole animals.

It must also be pointed out that the hyperalgesic effect of captopril is obtained in low doses, evidence of the high sensitivity of the key kinin-metabolizing enzyme to this inhibitor. Dipeptidyl-carboxydipeptidase exhibits less activity in enkephalin metabolism, as is shown by a higher level of doses needed for manifestation of the analgesic properties of captopril. The possibility likewise cannot be ruled out that when kinins accumulate, the binding of enkephalins with opiate receptors is disturbed, for we know that bradykinin inhibits binding of dihydromorphine with opiate receptors in the brain [15].

The experimental results supplement data in the literature indicating that captopril can potentiate and prolong the analgesic effect of morphine and the slowing of the respiration rate induced by it in mice [7, 10], and can potentiate the depressor effect of Met-enkephalin in rats [5]. In the light of our observations it can be tentatively suggested that the statement, made by some workers, that captopril has no effect on nociceptive responses [2, 8] can be explained by the use of small doses (about 0.1-1 mg/kg), when interaction between analgesic and hyperalgesic components is possible.

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