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MORPHINE-INDUCED MODULATION OF SCIATIC NERVE STIMULATION EVOKED BLOOD PRESSURE RESPONSES

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Abstract : Effect of i.v. morphine (1-2 mg/kg) on blood pressure changes evoked by sciatic nerve stimulation (SNS) were studied in chloralose anaesthetised cats. SNS gave a depressor, pressor or a biphasic BP response generally linked to the pararmeters of stimulation. Morphine produced marked attenuation of depressor and some facilitation of pressor response, suggesting a possible reciprocal relationship between depressor and pressor responses. Depressor response has been correlated with deep tissue or visceral pain mediated through A delta fibres and pressor response to cutaneous nociception involving C fibres or non nociceptive input via group II fibres. Involvement of medullary regions in differential modulation of these depressor and pressor response has been suggested.

Key words : nociception, pain, blood pressure, pressor response, morphine, depressor response

INTRODUCTION

The significance and physiological mechanisms underlying changes produced in cardio-respiratory responses evoked by peripheral nociceptive stimulation are not clearly understood. Pressor as well as depressor responses in blood pressure have been reported on such stimulations (1, 2, 3, 4, 5). One of the major factors determining the nature of the effect has been linked to the intensity of stimulation and the type of nerve fibres involved. Johansson (3) has reported that stimulation of unmyelinated C fibres causes hypertension and tachycardia while stimulation of A delta fibres causes bradycardia and hypotension.

In recent years electro-stimulation (6, 7, 8, 9, 10, 11) and or topical application of substances like morphine, 5-HT and glutamate (12, 13, 14, 15, 16 17, 18, 19,) have revealed brain stem descending influences modulating pain induced afferent activity accounting for the possible antinociception obtained. Most of these studies have utilized somato-motor reflex response like tail flick or hot plate test to evaluate the degree of antinociception. It is, however, known that somatic nociceptive fibres do evoke B.P. changes. Also, certain brain stem regions besides influencing autonomic responses form a part of the analgesia system (20, 21, 22, 23, 24, 25, 26, 27). It was, therefore, of interest to see the modulation of the peripheral nociceptive input induced cardio-vascular responses by morphine, a feature not reported earlier.

METHODS

Experiments were conducted on cats anaesthetised with i.p. chloralose (70 mgs/kg.). Femoral artery was cannulated for recording blood pressure and femoral vein for drug injections. Sciatic nerve was carefully exposed and sectioned. The central stump of the cut nerve was used for stimulation. The dissected area was kept moist and the nerve was kept immersed in liquid paraffin pool made by raising skin and muscle flaps around the nerve. Rectal temperature as well as temperature of the pool was maintained at 37°C.

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Blood pressure and respiration were recorded on a polyrite (INCO) using pressure and force transducers. Stimulation of the nerve was done with bipolar silver—silver chloride electrodes connected to the Nihon Kohden electronic stimulator (SEN 3201). Parameters of stimualtion used were: 3 to 10 volts, 0.5 to 5.0 msec pulse width, 50 Hertz for 15 seconds, categorized into two types i.e. low intensity stimulation (LISNS) consisting of 3-5 volts and 0.5 msec pulse width and high intensity stimulation (HISNS) consisting of 5-10 volts with pulse width of 5.0 msec. The frequency and duration of stimulation were kept the same for both LISNS and HISNS.

After taking the basal recording for a period of 10-15 min monitored for 2-3 min at every 5 min interval, the effects of SNS on BP and respiration were observed. Two to three readings both with LISNS and HISNS at five min intervel were recorded. This was followed by i.v. morphine administration in the dose of 1 to 2 mg/kg and once again the above observations of SNS were repeated every half hourly for the next two hours. In some animals i.v. naloxone (2 mg/kg) was given one hour after morphine injection and the observations continued for another 1-2 hours. Thus at least three recordings each before and after SNS as also after morphine and naloxone were taken to get some idea of the basal variability, if any, and also the temporal pattern of responses after different manipulations like SNS, morphine and naloxone treatment.

RESULTS

Anaesthetized cats showed considerable individual variability in their basal BP which ranged between 80-140 mm Hg. Absolute values of sciatic nerve stimulation (SNS) induced BP effects also varied from animal to animal. However, basal BP values as well as effects of SNS in the same animal remained fairly consistent.

In the present investigation in a group of seven cats subjected to LISNS, records obtained from five cats showed a fall in BP (depressor effect), mild pressor effect in one cat and pressor followed by depressor response in another cat. With HISNS three animals each gave pressor and depressor responses respectively and one showed a mild biphasic pressor followed by depressor change in BP (Fig. 1).

A total of 13 depressor and 3 pressor responses obtained with LISNS and HISNS taken together before the use of morphine were again similarly studied after giving morphine. The depressor res-

TABLE I : Blood pressuse responses.

	Depressor	*Pressor*	*No change*
Before Morphine	13 (−17.28)	3 (+9.56)	0
After Morphine	3 (−8.25)	9 (+16.71)	4

Value in paranthesis is mean % change

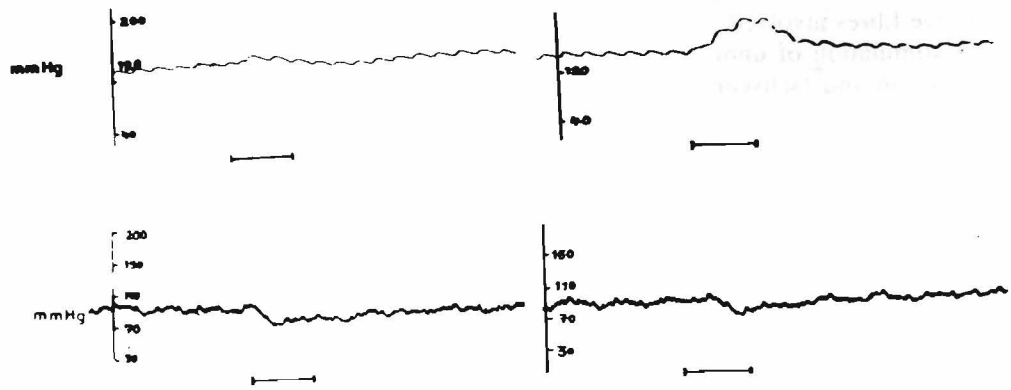

Fig. 1 : B.P. recordings of cats showing effects of low intensity (left half of the figure) and high intensity (right half of the figure) sciatic nerve stimulation. In one animal (upper tracings) only a pressor response and in another animal only a depressor response (lower tracings) was obtained with both types of stimulations.

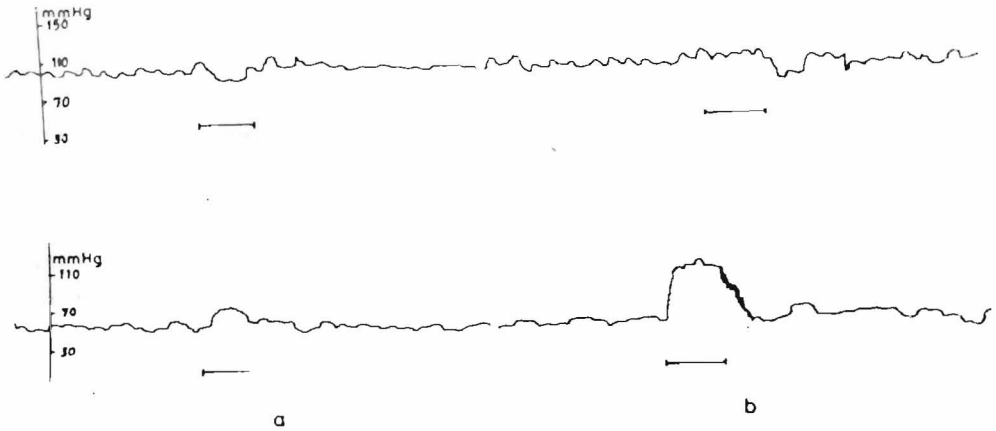

Fig. 2 : Effect of low and high intensity stimulation on B.P. before morphine (upper tracings) and 10 minutes after i.v. morphine (1 mg/kg) (lower tracings).

ponses obtained by sciatic stimulation varied from −8% to −38% while the pressor responses varied from +8% to +11% (Tab I). Observations on the effects of LISNS and HISNS within 10 min after injecting morphine (1-2 mg/kg, i.v.) revealed an increase in pressor (n=9) and a decrease in depressor (n-3) responses (Tab I). A record of one of the animals in which depressor response changed to a pressor response following the use of morphine is presented in Fig. 2.

Two animals in which the depressor response was markedly reduced after injection of morphine were later administered naloxone. This resulted in again eliciting depressor response, which however, was of a lesser magnitude as compared to the response before the administration of morphine.

The results of the study thus reveal that morphine supresses the depressor and facilitates the pressor responses evoked by sciatic nerve stimulation.

DISCUSSION

In the present study sciatic nerve stimulation produced depressor or pressor BP effects which were not specifically related to the stimulus intensity. Different combinations of depressor and the pressor effects were seen in different animals. Quite often only a depressor response was observed with both low as well as high intensity stimulation. Further it appears that inspite of individual variations in absolute values as also the type of effect, the low intensity stimulation generally produces depre-

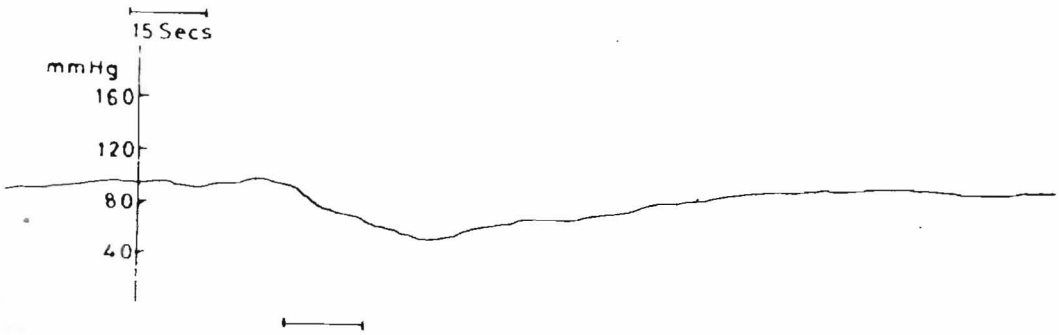

Fig. 3 : Effect of pinching toe muscles on blood pressure.

ssor and high intensity stimulation a depressor or pressor response. The fall or rise in blood pressure has been found to be generally related to the intensity of stimulation (1, 2, 3, 27) and is in the line with the results obtained in the present series. According to Johansson (3) the unmyelinated C fibre stimulation causes hypertension and tachycardia and myelinated A delta fibres stimulation produces hypotension and bradycardia. These result from the involvement of medullary centres, primarily provoking sympathetic stimulation or inhibition. The depressor response is attributed to prolonged activation of A delta (or group III) afferents and simultaneous decline of sympathetic discharge (1, 3). Milnor (28) showed that the depressor response is caused by rapid stimulation of high threshold C fibres or by low frequency stimulation of smaller myelinated fibres mediating deep pain. The present study confirms the contribution of nociceptive fibres in producing depressor response, as mechanical painful pinching of toe muscles resulted in decrease of blood pressure (Fig. 3). An attenuation of this depressor response was obtained by morphine (Fig. 2). The results of this study also show a facilitation of pressor response by morphine (Fig. 2), suggesting the possibility that the pressor response thus evoked from sciatic nerve may not be solely nociceptive in nature. Effect of naloxone in reversing the morphine induced attenuation of depressor response is expected. It is tempting to propose that pressor response is evoked by somatic afferents (Gr. III) participating in muscle exercise and facilitation of this response by morphine, or any other manipulation, may result inhibiting the nociceptically evoked depressor response.

While depressor response seems to be a nociceptically evoked somatoautonomic response, it is also quite likely that pressor response may be related to thermal nociception evoked by stimulation of skin by radiant heat (52°C) as reported in anaesthetised rats (29). In view of the existing reports on somatically evoked depressor and pressor response (29, 1 3, 28) it may be concluded that the depressor response evoked by muscle nerve stimulation involves Gr. III fibres carrying nociceptive afferents from deep muscle tissue somewhat similar to cardiovascular response produced during abdominal surgery, stretching or pinching of internal viscera. Hence depressor response functionally depicts deep or visceral pain. Pressor response on the other hand has been shown to be evoked by nociceptive somatic afferents from body surface particularly by noxious heat involving C fibres. The centres implicated are suggested to be located in the medulla, and the parabrachial area seems to be an important site where nociceptive projections from dorsal horn lamina I neurons have been demonstrated by HRP studies (30, 31).

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