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Cardiovascular reflexes mediated by sympathetic afferent fibers

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Abstract

In this paper the experimental evidence supporting the hypothesis that excitatory sympathetic reflexes may participate in the tonic control of the cardiovascular system is discussed. Positive feedback pressor sympathetic reflexes can be obtained with physiological distensions of the descending thoracic aorta in conscious dogs with all nerves intact in absence of any pain reaction. These excitatory reflexes interact with supraspinal regulatory mechanisms, inhibitory in nature. A massive excitation of cardiac sympathetic afferents, produced by intracoronary injections of bradykinin, also elicits a pressor reflex, without pain reactions. In the absence of anesthesia and recent surgery, the cardiovascular excitatory reflexes, subserved by sympathetic afferent fibers, can easily prevail. We suggest that negative and positive feedback mechanisms interact continuously to achieve the most adequate neural cardiovascular control.

Introduction

It is now well established that cardiovascular sympathetic afferent fibers can mediate cardiovascular reflexes that are mainly excitatory in nature and possess positive feedback characteristics [9,13,17,20]. However, what seems an even more

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important and increasingly likely possibility is that such excitatory reflexes are tonically active: accordingly, we have suggested that negative and positive feedback mechanisms, may interact continuously to achieve the most adequate neural regulation of the various cardiovascular performances. Obviously this corresponds to a new concept of neural cardiovascular control in which each specific hemodynamic condition, even those corresponding to the most stable resting state, would be associated with some degree of interaction of opposite tendencies, a biological example of a true dialectic process [13].

Four orders of evidence support this possible tonic function of reflexes mediated by afferents incorporated in sympathetic nerves: (i) afferent sympathetic fibers with receptor endings in the heart [2,10,13,18], in the aorta [16] or in the pulmonary veins [11] are spontaneously active under normal hemodynamic conditions and signal with precision mechanical events; (ii) cardiovascular excitatory reflexes can be obtained in fully innervated conscious animals with natural stimuli of physiological magnitude; (iii) these excitatory reflexes interact with other neural regulatory mechanisms inhibitory in nature; (iv) in the conscious state a massive excitation of cardiovascular sympathetic afferent fibers can be obtained in the absence of any pain reaction.

In this article, extending a previous one recently published [15], we shall analyze some additional facts which further support the validity of the points listed above.

Tonic impulse activity in the cardiovascular sympathetic afferent fibers

When acute electrophysiological experiments are performed in the presence of normal hemodynamic conditions, the cardiovascular afferent sympathetic fibers seem to be all spontaneously active and to signal normal hemodynamic events [2,13,16,18]. Furthermore, abnormal stimuli, such as coronary occlusion or intracoronary administration of bradykinin, were found to intensify only the impulse activity of afferent sympathetic fibers. There was no evidence of recruitment of silent afferents, provided the hemodynamic variables were within the normal range [2,10]. Some discrepancies in the interpretation of data obtained in some other laboratories [1,25,26] have been discussed elsewhere [10,13,14]: it suffices to say, in this context, that on the basis of our experimental findings, we concluded that cardiac sympathetic afferent fibers with a pure nociceptive function [1,4,25,26] are not likely to exist [12–14]. Instead it is our opinion that the 'intensity' mechanism that assumes that pain results from an excessive stimulation of receptive structures, is the most appropriate to account for the properties of the neural substratum subserving cardiac nociception [14].

Cardiovascular excitatory reflexes in fully-innervated conscious animals

A stretch of the thoracic aorta obtained with an implanted rigid core cannula covered by an inflatable rubber cylinder was used as an experimental tool for exciting, in the conscious animal, the aortic sympathetic afferent fibers [16]. What

should be emphasized here is that in the last series of experiments we directly measured with piezoelectric crystals the amount of aortic stretch performed. By increasing the diameter of the aortic segment surrounding the cannula by $9.6 \pm 0.4\%$ from 16 ± 1 mm we obtained a reflex increase in mean aortic pressure of $31 \pm 3\%$ from 100 ± 3 mm Hg, and in heart rate of $20 \pm 3\%$ from 91 ± 3 beats/min ($P < 0.01$) [20].

We also obtained a stimulus–response curve relating the increase in aortic diameter to the corresponding pressor response: the threshold for the reflex corresponded to a distension of about 2%, while a flattening of the curve was present beyond an increase in aortic diameter of 10%. In the conscious animal similar increases in aortic diameter accompany rises in arterial pressure within the physiological range. Thus the adequacy of the stimuli seems to be proved.

Interaction with inhibitory regulatory mechanisms

Two types of evidence are available on this point.

(a) The pressor sympathetic reflex just described was considerably increased in magnitude in animals in which the baroreceptive afferent fibers had been cut before the experiment [20]. The left panel of Fig. 1 indicates the arterial pressure and the heart rate response obtained in a dog with intact cardiovascular innervation. Under thiopental-sodium anesthesia and aseptic conditions the carotid sinus nerves were cut in the neck while the vagi were moved to a subcutaneous position. The middle

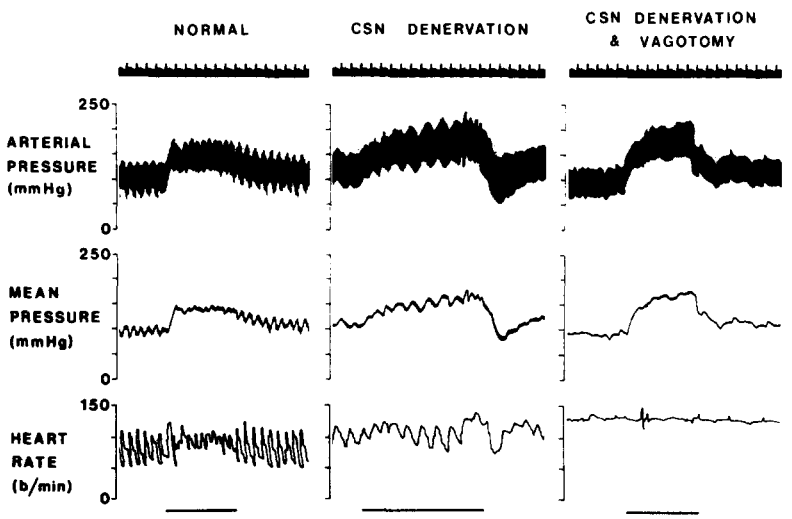

Fig. 1. Reflex effects of aortic distension (indicated by the bottom bars) on systemic arterial pressure and heart rate in a conscious dog. The left panel depicts the control response, the middle panel the response after sino-aortic denervation and the right panel the response after further sectioning of both vagi. Note the progressive increase of the pressor response that follows the denervation procedures. For other details see the text. (From Pagani et al., unpublished observations, and ref. 20, reproduced with permission.)

panel of Fig. 1 shows a response obtained 5 days after this additional surgery. Subsequently, under light transient thiopental-sodium anesthesia and local infiltration with Xylocaine both vagi were cut in the neck. The response to aortic stretch was again determined after a recovery period of 24–48 h (Fig. 1, right panel).

After vagotomy and carotid sinus denervation the aortic reflex-induced increase in mean arterial pressure ($49 \pm 8\%$ from 112 ± 7 mm Hg) was greater ($P < 0.05$) than that observed in the same dogs before denervation ($29 \pm 5\%$ from 100 ± 4 mm Hg) [20]. However, the heart rate response which was present before denervation ($23 \pm 3\%$ from 87 ± 4 beats/min) was no longer detectable presumably because of the higher baseline level (162 ± 9 beats/min) present after denervation [20].

(b) During the aortic stretch, the sensitivity of the baroreflex was significantly reduced [20]. Using the method of Smyth et al. [24], the slope of the regression line obtained by plotting the pulse interval against systolic arterial pressure during the pressure rise produced by the i.v. injection of phenylephrine (50 μg/kg) was used as an expression of baroreflex sensitivity. The control slope, obtained in the absence of aortic stretch, was relatively steep and averaged 18 ± 2 ms/mm Hg. In contrast, the slope obtained at the plateau of the pressor rise induced by aortic stretch was significantly ($P < 0.01$) less steep. The average reduction in baroreflex sensitivity in the group of animals was $57 \pm 7\%$ ($P < 0.01$).

Such a possibility had already been suggested by acute experiments carried out with electrophysiological techniques [23].

Excitation of cardiovascular sympathetic afferents leading to a pressor reflex in absence of any pain reaction

The aortic stretches described in the preceding paragraph were never accompanied by any overt behavioural change of the animals such as agitation, sudden movements or vocalizations, suggestive of a pain reaction. However, this could have been the result of the magnitude of the stimuli, which were most often if not always confined to the physiological range of aortic diameter changes [19].

We have recently developed a technique for exciting the cardiac sympathetic afferent fibers in conscious dogs with intracoronary injection of bradykinin. In fact, this substance that is released by the acutely ischemic myocardium, excites both vagal [8] and sympathetic [1,5,10,26] cardiac afferents and as far as the latter are concerned such an excitation is likely to be maximal [1,5,10].

In this case as well, under anesthesia and aseptic conditions, dogs were prepared for this study by implantation of a small silicone catheter in either the left anterior descending or circumflex coronary artery, and also prepared for the measurement of arterial pressure, left ventricular pressure (LVP), LVdP/dt and heart rate (HR) [21].

Experiments were performed 1–3 weeks later, when the animals had totally recovered from surgery. In the conscious dog the intracoronary injection of bradykinin (100 ng/kg) produced a consistent pressor response in absence of any pain reaction.

After a latency of about 15 s, significant ($P < 0.01$) reflex increases in mean

arterial pressure ($31 \pm 3\%$ from 85 ± 2 mm Hg) and in heart rate ($34 \pm 3\%$ from 84 ± 9 beats/min) were observed, together with increases in LVP and $LVdP/dt_{max}$ [21]. In several trials, doses of bradykinin up to 3 μg/kg were injected into the cannulated coronary artery without eliciting pain reactions. Incidentally, at these very high doses the vasodilatory hypotensive direct effect of the drug was the first response to be observed and preceded a hypertensive rebound. The following short comments appear necessary concerning these data.

The intracoronary injection of bradykinin in anesthetized cats [12] elicited either an excitatory cardiovascular and sympathetic reflex mediated by cardiac sympathetic afferent fibers or an inhibitory reflex mediated by vagal afferents, the type of response being consistent in each individual animal: in short the prevailing reflex response was likely to be dependent upon the interaction of opposite influences mediated by the simultaneous activation of cardiac vagal and sympathetic afferents. Thus the conscious state appears to provide advantage to the neural mechanisms subserved by sympathetic afferents [13].

On the basis of the 'intensity' theory for cardiac pain [14] it is hard to explain the absence of pain reactions in concomitance with a massive excitation of cardiac sympathetic afferents. However, this finding is even more surprising in relation to a theory of 'specificity' which assumes that pain is the product of the excitation of a well-defined nociceptive apparatus, the functional characteristics of which make it responsive only to a limited class of events, i.e. the stimuli that are 'noxious' [22].

According to this view, the intracoronary administration of large doses of bradykinin in conscious animals should produce pain through the activation of silent afferent fibers purely nociceptive in function. However, this was not observed in experiments on healthy conscious dogs with intracoronary administration of bradykinin at doses two orders of magnitude greater than the one needed to elicit clear excitatory reflexes [21] and massive excitation of sympathetic afferents [10].

Our hypothesis for such a finding is the following. Pain would result from the intense excitation of a spatially segregated contingent of afferent fibers: only in these conditions would the 'break-through' occur, overcoming inhibitory modulating mechanisms [27], thus leading to the conscious experience of pain.

It is a fact that a hypertensive crisis, although often associated with an unpleasant feeling, does not elicit pain in humans or clear pain reactions in animals, which show at most a state of restlessness. Yet during a marked hypertension very many cardiovascular sympathetic afferents are excited. In conclusion, the excitation with bradykinin of cardiac sympathetic afferents would be too diffuse and would not simulate the various and different mechanical and chemical peculiarities present locally during myocardial ischemia. That the causes are subtle is clearly suggested by the many cases of myocardial ischemia with no pain in humans [3].

In conclusion we think that to propose a predominant nociceptive function [1,6] for cardiac sympathetic afferents seems now untenable. Their reflex function is not only a well-proved fact, but is a more likely hypothesis for their biological development: indeed it is difficult to imagine the need for a specific alarm system for signalling cardiac pain in animals [14].

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