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FUNCTIONS OF AFFERENTS IN CARDIOVASCULAR SYMPATHETIC NERVES

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ABSTRACT

This paper contains data and discussion of the role of afferents in the sympathetic trunks from the cardiovascular complex that evoke autonomic reflex action. A description is given of these cardiovascular reflexes induced by afferents of the sympathetic trunks in neurally intact as well as spinal animals. A positive feedback hypothesis is also proposed.

INTRODUCTION

During the last decade and a half it has been demonstrated repeatedly that the afferent fibers in sympathetic nerves with cardiovascular endings (sympathetic afferents; see Malliani [16]) have a tonic activity [4,6,9,14,16,18, 23,27,40,41] and subserve a reflex function of physiological significance [3,12,17,20–22,24,29]. Although such properties may appear not at all surprising for an afferent system, it should be recalled that until recently a general view was that the cardiovascular sympathetic afferents have an exclusive nociceptive role [11] and hence do not participate in the neural regulation of cardiovascular functions. It also has been held generally that only the cardiovascular afferents projecting directly upon the supraspinal structures conveyed important information from reflexogenic areas. These two conclusions, however, were revised [5,17,20,23,28,32,38]. In this article we shall analyze some general functional properties of sympathetic cardiovascular afferents.

SIMULTANEOUS ACTIVATION OF VAGAL AND SYMPATHETIC CARDIAC AFFERENTS AND REFLEX EFFECTS

Vagal and sympathetic sensory endings in the heart can be excited simultaneously. It is sometimes claimed that in such a case the vagally-mediated depressor influences invariably dominate [2,7]. However, the opposite can also be true, depending on the experimental conditions and the nature of the stimuli.

In recent experiments by our group [15], the intracoronary administration of bradykinin in neurally intact anesthetized cats produced two different responses, each type being consistent for any given animal. In a majority of cats, a significant reflex increase in the efferent sympathetic nerve activity to the heart, in arterial pressure and in left ventricular (LV) dP/dt_{max} was elicited. In a minority of animals, bradykinin produced a slight increase in the efferent sympathetic nerve activity associated with a significant decrease in arterial pressure and in LV dP/dt_{max}. After vagotomy, an excitatory reflex was present in all animals, increasing significantly efferent sympathetic discharge, arterial pressure and LV dP/dt_{max}. Thus, intracoronary bradykinin induced a complex neural and hemodynamic reflex response [34] characterized by a predominance of excitatory components.

Our experiments confirmed previous findings by Staszewska-Barzak et al. [39] obtained with epicardial applications of the drug and showed that the excitatory reflex is not dependent on a given way of administering the drug as has been suggested [7].

The relevance of these data is that they provide basis for a new interpretation of the origin of pressor responses that often accompany, in man, episodes of transient myocardial ischemia even in absence of pain [8,13,25] or during the very early stages of myocardial infarction [31,42]. Indeed, in our first description of an excitatory sympathetic reflex elicited during coronary occlusion in anesthetized cats [24], we hypothesized that such a reflex could on one hand oppose the reduction in myocardial contractility induced by ischemia but, on the other hand, could also increase oxygen consumption or facilitate arrhythmias. The evidence since then has been continuously growing that neural mechanisms are importantly involved in life-threatening arrhythmias [1,35,36]. Pathophysiological reflexes have little to do with protective effects, as still claimed [10].

EXCITATORY CARDIOVASCULAR REFLEXES MEDIATED BY SYMPATHETIC AFFERENTS AND PAIN

It was an initial legitimate suspicion that a stimulus capable of consistently activating cardiovascular sympathetic afferents and thereby inducing an excitatory hemodynamic reflex could be perceived as painful by the alert animal. Obviously, were this to be true, these reflexes should have been considered only as a part of a general response to pain. This possibility had to be tested.

Under general anesthesia and aseptic conditions a 6—8 cm incompressible cannula covered by an inflatable rubber cylinder was positioned in the descending thoracic aorta of dogs [19]. After a recovery period of 1—2 weeks, the implanted cylinder was inflated in the conscious dog, causing distension of a short segment of the aorta, without interfering with aortic blood flow. This stretch, in the absence of pseudoaffective reactions, produced a sustained and significant increase in mean arterial pressure and heart rate.

Above a given threshold level, progressive increases in the pressor response were obtained by augmenting the distension. The reflex nature of the pressor response was proved by its disappearance after alpha-adrenergic blockade (phentolamine, 1.0 mg/kg body weight i.v.). The reflex tachycardia was abolished by combined vagal and beta blockade (atropine or scopolamine, 0.2—0.3 mg/kg and propranolol, 1 mg/kg, i.v.).

The adequacy of the stimulus must be considered. Stretches similar to those used in the experimental trials increased the aortic diameter in post-mortem control experiments by about 7—10%; this increase is in the range of changes in diameter accompanying physiological increases in arterial pressure. Thus, excitatory cardiovascular reflexes mediated by sympathetic afferents do not utilize a neural substrate exclusively nociceptive in function.

In the unanesthetized primate it was recently found by Randall et al. [33] that anterior descending coronary artery occlusion was always accompanied by increases in heart rate and LV dP/dt_{max} and that these changes were unlikely to reflect a simple pain response as suggested by the behavior of the animals and by the fact that the occlusion of the left circumflex produced a depressor response.

These observations lead to the last point that we wish to analyze.

ARE EXCITATORY CARDIOVASCULAR REFLEXES MEDIATED BY SYMPATHETIC AFFERENTS PRESENT IN THE NEURALLY INTACT ANIMAL?

A positive answer is already implicit in the experiments just described. However, some more discussion is appropriate. In fact, it should be pointed out that a similar stretch of the descending aorta in the anesthetized cat [12] produces a marked excitatory reflex only after the interruption of supraspinal buffering mechanisms. Thus we were the first to doubt the significance of these reflexes in the intact animal. Experiments on unanesthetized conscious animals are instead in favor of the hypothesis that anesthesia and acute studies have highly emphasized the importance of supraspinal homeostatic mechanisms [19,38].

Reflexes mediated by cardiovascular sympathetic afferents, although they can *also* be present in spinal animals, involve supraspinal structures as well. This point was first demonstrated by acute experiments in which the stimulation of cardiac sympathetic afferents was found capable of inhibiting the discharge of cardiac vagal efferent fibers and of interfering with responses evoked by baroreceptive mechanisms [37]. Moreover, this fundamental property was also demonstrated in experiments performed on the conscious dog,

in which we observed a reduction of the baroreflex due to sympathetic afferent discharge during aortic stretch [19].

THE POSITIVE FEEDBACK HYPOTHESIS

Our experiments revealed that the excitatory reflexes mediated by cardiovascular sympathetic afferents do not depend on pain mechanisms but seem to reveal the existence of positive feedback mechanisms [19]. In fact, as a consequence of the pressure—diameter relationship of the aortic wall [30], an aortic stretch is likely to simulate the effects of an increase in mean aortic pressure [18]: this stimulus produced a reflex increase in arterial pressure. It is obvious that the same stimulus applied to the carotid sinus would produce an opposite response.

These positive feedback mechanisms should obviously be conceived as part of those complex regulatory mechanisms that are the result of multiple and independent peripheral loops and various levels of central integration. Negative feedback mechanisms seem quite often to be the effective controllers in overall cardiovascular regulation: but even in this case, positive feedback mechanisms could be of paramount importance in determining the range of operation, the gain and the stability. There are, however, physiological and pathological conditions in which the efferent sympathetic activity seems to escape any restriction, as in exercise, emotion, and arterial hypertension.

Our hypothesis is that peripheral sympatho-sympathetic loops exhibiting positive feedback characteristics may importantly participate in the hemodynamic states characterizing these conditions.

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