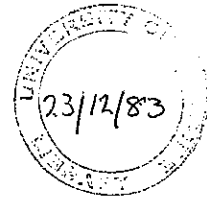


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HYPERTENSIVE MECHANISMS OF BRADYKININ AND ANGIOTENSIN

by

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A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

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MARCH 1983

PREFACE

Bradykinin is a naturally occurring nonapeptide which is a powerful vasodilator compound, characteristically causing hypotension and a tachycardia on systemic administration. In addition to its direct peripheral vasodepressor action, it also has an equally powerful central action to cause hypertension and a tachycardia which are mediated, in part, by an action on the autonomic nervous system.

The experiments reported in this thesis were conducted to determine more precisely the central site of action of bradykinin and to investigate a number of possible mechanisms which could contribute to the cardiovascular response to centrally-administered bradykinin in the morphine and chloralose anaesthetised greyhound.

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SUMMARY

Since its discovery in the early 1900's, bradykinin has been described as a potent dilator of arterioles in the peripheral circulation as well as in specific vascular beds, e.g. the renal, cerebral and coronary circulations. Subsequent to the widespread vasodilation (which is a direct effect of bradykinin on vascular smooth muscle) that occurs following systemic administration, arterial blood pressure decreases and the resultant stimulus to the baroreceptor reflex mechanisms causes an increase in heart rate and cardiac output. In the morphine and chloralose anaesthetised greyhound, the mechanism of the tachycardia is primarily withdrawal of vagal tone to the heart. The alterations in the cardiovascular parameters that were measured are consistent with previously published work, although the precise mechanism of the increase in heart rate in the greyhound is different to the mechanism in other animals, probably because of the relatively high vagal tone to the heart in the morphine and chloralose anaesthetised greyhound compared with other smaller animals, e.g. rats, rabbits and cats, where an increase in sympathetic activity to the heart seems to be an important mechanism to cause an increase in heart rate.

In addition to its vasodepressor action when administered systemically, bradykinin has also been shown to have a powerful hypertensive action when administered into either the cerebral circulation (via a carotid artery) or directly into the cerebral ventricles. However, the mechanism of this effect of bradykinin is not clear, although there is evidence to suggest involvement of both α and β adrenoceptors. The central site of action of bradykinin has also not been localised, so the experiments described in this thesis were conducted to determine the central site of action and to characterise, in more detail, the mechanism(s) of the

hypertensive response to vertebral artery and carotid artery infusions of bradykinin.

The results of the experiments reported in Chapter 2 indicate that the autonomic nervous system is involved in the hypertensive response and that while selective blockade of α and β adrenoceptors modifies the cardiovascular responses, the vagus nerves are of major importance in determining the responses obtained.

Ablation of the area postrema abolished the central pressor effect of both vertebral and carotid artery bradykinin indicating that the integrity of this area is required for the central pressor effect of bradykinin. It has also been demonstrated that bradykinin has no direct effect on the heart to contribute to the increase in heart rate, so bradykinin is gaining access to central structures to cause the tachycardia. It is also probable that a central cholinergic mechanism and the formation of prostaglandins are intimately involved in the centrally-mediated response to bradykinin and that a direct action in the carotid sinus region or the release of vasopressin do not contribute to the response to centrally-administered bradykinin.

Angiotensin II also has a specific central action mediated via the area postrema to increase arterial blood pressure and while the precise mechanism of action of angiotensin II is still not known, it has recently been suggested that a central opiate mechanism is involved in this response. The results presented in the final section of this thesis indicate that central opiate mechanisms are not involved and also that the greyhound utilises different pathways to other species, even the mongrel dog, in which opiate mechanisms have been shown to be involved in the centrally-mediate response to angiotensin II. While

vertebral artery angiotensin II and bradykinin both act through the area postrema to inhibit cardiac vagal tone, the cardiovascular responses to these peptides show major differences when administered either intravenously or via a carotid artery.