Augmentation of Vagal Reflex Bradycardia by Central $\alpha_2$-Adrenoceptors in the Cat

Hisato Kitagawa* and Alexander Walland

Department of Pharmacology, Boehringer Ingelheim KG, D-6507 Ingelheim, Federal Republic of Germany

Summary. Vagal reflex bradycardia was induced in anaesthetized cats with high level spinal axotomy by electrical stimulation of either the carotid sinus nerves or a depressor nerve. In both preparations reflex bradycardia increased with the rate of stimulation. Injection of 1 µg/kg clonidine into a lateral cerebral ventricle augmented reflex bradycardia in response to carotid sinus nerve stimulation while the same dose of clonidine was ineffective when given intravenously. The antagonistic effect of intracerebroventricular yohimbine (50 µg/kg) indicated that the effect of clonidine was due to its $\alpha_2$-agonistic action. In contrast to carotid nerve stimulation the reflex bradycardia in response to depressor nerve stimulation was unaffected neither by intracerebroventricular injection of clonidine (2 µg/kg) nor by yohimbine (100 µg/kg).

It is concluded that in the cat, the function of the central parts of the baroreceptor reflex which originate from the carotid sinus area is augmented by stimulation of $\alpha_2$-adrenoceptors while the function of those parts originating from the aortic area is not.

Key words: Vagal reflex bradycardia - Carotid sinus nerve stimulation - Depressor nerve stimulation - Clonidine - Yohimbine - Cat

Introduction

Intravenous injection of the $\alpha$-adrenoceptor agonist clonidine increases vagal reflex bradycardia in response to baroreceptor stimulation by the pressor effect of intravenous adrenaline, noradrenaline or angiotensin in anaesthetized dogs pretreated with $\beta$-adrenolytic or adrenergic neuron blocking drugs (Robson and Kaplan 1969; Robson et al. 1969). The main site of this action is central because the injection of small doses of clonidine, which are ineffective when given intravenously, into the cisterna magna of anaesthetized or conscious dogs causes an augmentation of vagal reflex bradycardia elicited by intravenous injection of noradrenaline, angiotensin, or by mechanical compression of the abdominal aorta (Kobinger and Walland 1971, 1972; Walland et al. 1974). Decerebration experiments localized the responsible adrenoceptors in the medulla oblongata (Kobinger and Pichler 1975). However, other studies (Laubie et al. 1976) in dogs with $\beta$-adrenoceptor blockade reveal an augmentation of reflex bradycardia in response to electrical stimulation of the carotid sinus nerve by injection of clonidine into the vertebral artery. In contrast to the dog, the role of central $\alpha$-adrenoceptors in the vagal baroreflex bradycardia is less clear in the cat. Kobinger and Pichler (1978) reported clonidine to have little effect on vagal reflex bradycardia elicited by intravenous injection of pressor substances. Connor et al. (1981) found the duration rather than the magnitude of reflex bradycardia in response to intravenous angiotensin to be increased by intracisternal clonidine in cats pretreated with propranolol. On the other hand, Antonaccio and Halley (1976) reported on a marked enhancement of reflex bradycardia in response to noradrenaline under pretreatment with propranolol.

Because of these discrepancies, we wanted to reinvestigate in cats whether central $\alpha$-adrenoceptors modulate the vagal reflex bradycardia evoked by electrical stimulation of baroreceptor nerves.

Methods

Experiments were performed in mongrel cats of either sex weighing 2.6–3.8 kg being anaesthetized with chloralose (80 mg/kg). A glass cannula was introduced into the trachea after tracheotomy for artificial positive pressure ventilation. Using a stereotactic device (La Précision Cinématographique, Paris, France), the tip of a rubber-capped steel cannula was lowered into the left lateral ventricle. The cannula was fixed to the skull and served as a guide for a 20 gauge needle through which drugs were injected. According to the atlas of Snider and Nimer (1964) the following coordinates were used: frontal +12 mm, left lateral 4 mm and vertical +12 mm. The ventricular position was confirmed at the end of the experiment by injecting a solution of Evans blue. The position was considered to be correct when dye appeared immediately afterwards in the open cisterna magna. For high-level spinal axotomy the cats were fixed on the operation table in the prone position. The first and second vertebrae were exposed. A blunt but complete transection of the spinal cord was performed with a pair of bent forceps at C1/C2. The artificial opening was closed by pressing a cone of plasticene into the spinal canal. The preparation of nerves and the actual experiment were done in the supine cat. In order to maintain free access to the vertebral cannula, a special head support was used.

Send offprint requests to A. Walland at the above address
* Present address: Kawanishi Pharma Research Institute, Nippon C. H. Boehringer Sohn Co., Ltd. 103 Takada, Yato, Kawanishi Hyogo, Japan

0028-1298/82/0321/0044/$01.00

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The carotid sinus nerves were interrupted bilaterally by severing all nerves emerging from the bifurcations of the carotid arteries. The depressor nerves were identified by following the branches, which run from the superior laryngeal nerves to the vagosympathetic trunks. The vagosympathetic portions of the depressor nerves were separated in the distal direction over a length of about 10 mm and severed distally. The central stump of the left depressor nerve was placed on a bipolar electrode with platinum contacts being 2 mm apart. The whole operation field was covered with moistioned gaze.

Results

Vagal Bradycardia in Response to Stimulation of a Depressor Nerve

In a series of 5 cats, 90–120 min after spinalization and stabilization of the circulation, the mean arterial blood pressure was 75 ± 14.2 mmHg and the heart rate was 113 ± 6.9 beats/min. The intracerebroventricular injection of 2 μg/kg clonidine did not cause any changes in these parameters (maximal values: 76 ± 11.8 mmHg and 113 ± 7.8 beats/min). The intravenous injection of 2 μg/kg clonidine, which was given 3 h later, caused a significant (P < 0.05) increase in blood pressure (maximum: 130 ± 15.2 mm Hg) which returned to control level within 20 min. There was no significant change in heart rate (minimum: 103 ± 8.9 beats/min).

The unilateral stimulation of a depressor nerve induced a reproducible reduction in heart rate which was nearly linear with the logarithm of the stimulation rate (Fig. 1). Neither the intracerebroventricular (Fig. 1) nor the intravenous (not shown) injection of 2 μg/kg clonidine caused any relevant change in the relationship between the maximal decrease in heart rate and the rate of stimulation.

In an other series of 5 axotomized cats with an initial blood pressure of 75 ± 7.2 mm Hg and a heart rate of 131 ± 17.5 beats/min, an injection of 100 μg/kg yohimbine was given intracerebroventricularly. Yohimbine did not cause any significant haemodynamic changes (maximal blood pressure: 82 ± 9.7 mm Hg; minimal heart rate: 124 ± 16.6 beats/min).

Similarly the rate-dependent bradycardia in response to depressor nerve stimulation was not influenced by the injection of yohimbine.

Vagal Bradycardia in Response to Carotid Sinus Nerve Stimulation

A group of 7 cats with high level spinal axotomy and severed depressor nerves but intact carotid sinus nerves received an intracerebroventricular injection of 1 μg/kg clonidine and 1 h later an injection of 50 μg/kg yohimbine by the same route. In 5 of these 7 cats 1 μg/kg clonidine was injected intravenously 40 min before the central administration of clonidine. At the start of the experiment, the mean blood pressure was 82 ± 5.4 mm Hg and the heart rate was 125 ± 9.8 beats/min. The maximum blood pressure after intravenous clonidine was 114 ± 11.0 mm Hg. All the other administrations did not cause significant changes. At the end of the experiment, blood pressure was 72 ± 5.0 mm Hg and heart rate was 100 ± 7.2 beats/min.

Bilateral electrical stimulation of the carotid sinus nerves in situ elicited vagal reflex bradycardia which increased with the rate of stimulation. The relationship between the extent of bradycardia and the logarithm of stimulation rate appeared to be sigmoid (Fig. 3).

Intravenous injection of 1 μg/kg clonidine did not influence reflex bradycardia induced by carotid sinus nerve stimulation.

In contrast to the intravenous injection, the intracerebroventricular injection of 1 μg/kg clonidine caused a distinct potentiation of reflex bradycardia as can be seen in the original tracings of Fig. 2 and in the averaged results of Fig. 3.

Fig. 1. Dependence of vagal reflex bradycardia on stimulation rate, in response to unilateral electrical depressor nerve stimulation in 6 anaesthetized cats with high level spinal axotomy, before and after intracerebroventricular injection of 2 μg/kg clonidine. Stimulation was performed with direct current pulses (1 ms duration, 5 V) with frequencies of 1 – 32 Hz for 15 s at intervals of 3 min. Mean values ± S.E.M. of the maximal decrease in heart rate of two series of stimulation before (O) and two series after clonidine (●) are plotted against the logarithm of stimulation rate. Statistical evaluation: Student’s paired t-test, n.s.: P > 0.05.