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INFERIOR CARDIAC NERVE ACTIVITY IN THE CAT DURING SUPERFUSION OF THE VASCULARLY ISOLATED CAROTID SINUS WITH PROPRANOLOL

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1 Inferior cardiac nerve activity in 9 cats was in inverse relationship to the pressure maintained in the systemically isolated and perfused carotid sinus.

2 Perfusion with propranolol produced no change in this relationship at a concentration of 5.0 μg/ml, but abolished it at 50.0 μg/ml.

3 The results suggest that concentrations of propranolol which have been reported to enhance the sensitivity of the carotid sinus to pressure do not enhance one neurophysiological component of the reflex depressor response.

Introduction

The effects of propranolol on the gross haemodynamic parameters associated with the carotid sinus depressor reflex have been well established (Prichard & Gillam, 1969), but little attention has been given to the individual neurophysiological components of the reflex (Haeusler, 1974). Recently, propranolol (5.0 μg/ml) has been found to enhance carotid sinus nerve activity during constant pressure, or flow perfusion of the semi-isolated sinus, possibly through modifications of sinus distensibility (Tuttle & McCleary, 1978). Simultaneous recordings from a sympathetic trunk should show an inhibitory enhancement during exposure of the carotid sinus to propranolol.

The present experiments were designed to test this hypothesis by recording from the inferior cardiac nerve of the right stellate ganglion while infusing propranolol into the carotid sinus.

Methods

Nine cats weighing 3 to 4 kg were selected at random and anaesthetized with 0.7 ml Dial Urethane (Ciba-Geigy Co., Summit, NJ). The right and left carotid sinus regions were isolated from the general systemic system leaving the carotid sinus nerves intact (Tuttle & McCleary, 1978).

The right stellate ganglion was exposed retropleurally, care being taken not to perforate the pleura. The inferior cardiac nerve was then cut distally and placed on a bipolar Ag-AgCl recording electrode. An oxygenated (95% O_2, 5% CO_2) saline perfusion solution was used to equilibrate the sinus at 50 mmHg. Three recordings were then made at pressures of 100, 150 and 200 mmHg. After each recording, sinus perfusion pressure was returned to 50 mmHg. Propranolol (Inderal, Ayerst Company, 5.0 or 50.0 μg/ml) was then added to the perfusate and, after 15 min, the series repeated.

Statistical methods

A calculation of activity was made in each 'burst' associated with respiration by counting individual spikes under a 15× magnifier. Controls were first established at 50 mmHg and the pressure was then elevated in the sinus and counts were made in 4 bursts beginning with the second following the increase in pressure.

Statistical comparisons (Student's *t* test) of average activity per burst, before and after increasing pressure, and after exposure to two propranolol concentrations were then made by pooling the data for each of the 9 animals for each period of the protocol.

Results

In each of the 9 cats, the discharge from the right inferior cardiac nerve was coupled, 'burst fashion', with the inspiratory phase of the respiratory cycle (insert, Figure 1). During the control period in each cat, the total activity per burst was relatively constant, but between cats it varied by a factor of 2 to 3. Any dimunition of total discharges within a respiratory

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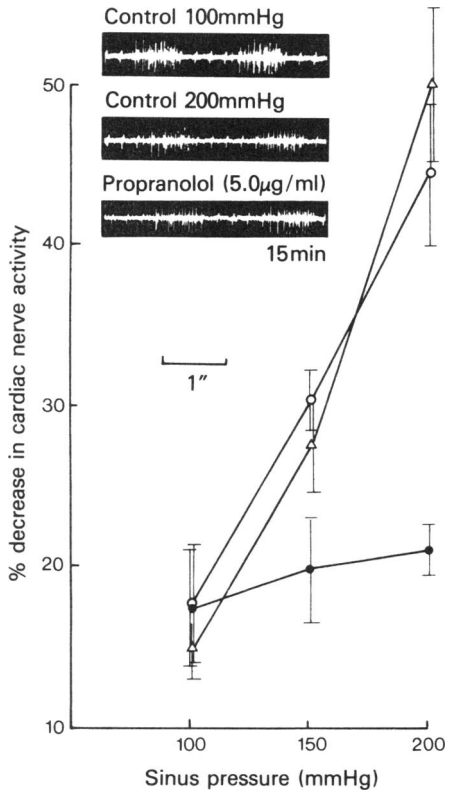

Figure 1 Percentage reduction of inferior cardiac nerve activity in 9 cats produced by increasing carotid sinus pressure from 50 mmHg to 100, 150 and 200 mmHg: (○) controls; (△) 15 min after beginning sinus perfusion with 5.0 μg/ml of propranolol; (●) 15 min after exposure to 50.0 μg/ml. In the upper left of this figure are shown recordings from the inferior cardiac nerve in one cat during perfusion of the sinus region at 100 and 200 mmHg before, and at 200 mmHg after exposure to 5.0 μg/ml of propranolol.

'burst' occurred within 2 to 3 s after raising sinus pressure. With increasing pressure, the respiratory bursts became shorter and less dense as individual fibre populations were lost rather than individual frequencies reduced (insert top of Figure 1).

Although there were large individual variations in total activity between cats, the percentage reduction in activity, calculated from the total activities before and after increasing sinus perfusion pressure, were remarkably similar and the statistical variations quite low (open circles, Figure 1). Plotted together, an inverse relationship between sinus pressure and percentage change in inferior cardiac nerve activity was obtained.

Fifteen min after exposing the sinus to an infusion of propranolol (5.0 μg/ml), total spike activity at 50 mmHg was unchanged and raising sinus pressure to 100, 150 and 200 mmHg produced reductions in inferior cardiac nerve activity similar to pre-drug controls (Figure 1; triangles).

Following a washout period (5 to 15 min) with drug-free solution, propranolol (50.0 μg/ml) was again added to the superfusion system. No difference in total activity was recorded at 50 mmHg when compared with the other two groups. However, with increasing pressure, there was a smaller percentage reduction in cardiac nerve discharge. At sinus pressures of 150 and 200 mmHg, the percentage reduction was significantly less than that of the control and 5.0 μg/ml propranolol groups at the same pressures (Figure 1; closed circles).

Discussion

In the present studies, the right inferior cardiac nerve was used as a model for a sympathetic efferent nerve (Bronk, Ferguson, Margaria & Solandt, 1936) although it is generally believed that it is the vagus which is the primary route for the negative chronotropic component of the depressor reflex (Heymans & Neil, 1958). However, the relationship demonstrated here between sinus pressure and inferior cardiac nerve activity shows that a proportional reduction of sympathetic outflow to the heart occurs during sinus pressor loading regardless of whether its effect is subservient to that of the vagus.

The results suggest that the inverse relationship between sinus perfusion pressure and inferior cardiac nerve activity was not modified by concentrations of propranolol (5.0 μg/ml) which, under similar conditions, produced significant increases in carotid sinus nerve activity and resistance to stretch (Tuttle & McCleary, 1978). Higher concentrations of propranolol (50.0 μg/ml) did abolish the sinus pressure-cardiac nerve relationship, but this concentration is near the antiarrhythmic level where local anaesthetic effects may predominate (Davis & Temte, 1968; Coltart & Meldrum, 1970) in the sinus to reduce sinus nerve activity so that there would be no decrease in cardiac nerve discharge. Although the effects of propranolol on the cardiac nerve response to changes in sinus pressure may be explained thus, it is more difficult to understand why a lower concentration, which has been reported to enhance sinus receptor activity, did not facilitate the depressor response in the cardiac nerve.

One explanation may be that the type of fibre contributing to the enhancement of the carotid sinus nerve discharge by propranolol impinges on central vasomotor structures that ultimately have little effect

on events recorded at the stellate ganglion. Landgren (1952) proposed that two types of fibres responded with activity in the sinus, according to the level of distensibility of the sinus wall. Should the larger fibres subserve an ultimate destination and purpose different from that of the smaller, such as impingement upon vagal centres, any selective enhancement of their activity by propranolol might be lost at the sympathetic centres. It is of interest to note that the larger spike populations in the sinus nerve were those recruited in previous studies by both increasing sinus pressure and by propranolol (Tuttle & McCleary, 1978).

It is conceivable that both the effects observed in the present study are due to selective interactions of propranolol with a fibre population only secondarily involved with sympathetic outflow at the level of the stellate. This also may explain why the high concentrations of propranolol produced no change in the depressor reflex at 50 and 100 mmHg, but significant changes at 150 and 200 mmHg.

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References

BRONK, D., FERGUSON, I.R., MARGARIA, R. & SOLANDT, D.Y. (1936). The activity of the cardiac sympathetic centers. *Am. J. Physiol.*, **117**, 237–249.

COLTART, D.J. & MELDRUM, S.J. (1970). The effect of propranolol on the human and canine transmembrane potential. *Br. J. Pharmac.*, **40**, 148–149.

DAVIS, L.D. & TEMTE, V.J. (1968). Effect of propranolol on the transmembrane potentials of ventricular muscle and Purkinje fibres of the dog. *Circulation Res.*, **22**, 661–677.

HAEUSLER, G. (1974). Further similarities between the action of clondine and a central activation of the depressor baroreceptor reflex. *Naunyn Schmiedeberg's Arch. Pharmac.* **285**, 1–14.

HEYMANS, C. & NEIL, E. (1958). *Reflexogenic Areas of the Cardiovascular System.* New York: Little Brown Co.

LANDGREN, S. (1952). On the excitation mechanism of carotid baroreceptors. *Acta physiol. scand.*, **26**, 1–34.

PRICHARD, B.N.C. & GILLAM, P.M.S. (1969). Treatment of hypertension with propranolol. *Br. med. J.*, **i**, 7–15.

TUTTLE, R.S. & MCCLEARY, M. (1978). A mechanism to explain the antihypertensive action of propranolol. *J. Pharmac. exp. Ther.*, **207**, 56–63.

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