REGULATION OF THE CARDIAC RHYTHM DURING THE DEPRESSOR BAROREFLEX

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KEY WORDS: baroreflex; sympathetic and parasympathetic regulation of the heart.

Function tests based on comparison of the character of baroreflex regulation of the heart rate (HR) in healthy subjects and patients have recently become widely adopted in clinical investigations [7, 11, 12]. So far, however, no general agreement has been obtained on the efferent mechanisms of the increase in HR during the depressor baroreflex. On the basis of a pharmacological analysis of these mechanisms some workers [5] have concluded that the reflex tachycardia in response to a fall of arterial pressure in anesthetized dogs is purely sympathetic in nature. The results of similar investigations on man [6, 8] led the same investigators to conclude that the parasympathetic innervation plays the dominant role in the baroreflex rise in HR. In another investigation [10] on unanesthetized dogs, a compromise point of view was expressed and a mixed mechanism of the chronotropic component of this reflex was postulated.

The object of this investigation was to analyze one of the causes of this disagreement and to determine how the chronotropic reaction depends on the original heart rate.

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized cats weighing 3-4.4 kg. Under pentobarbital anesthesia (40 mg/kg) polyethylene catheters were introduced into the carotid artery and external jugular vein. The peripheral end of the catheters was connected to miniature cocks, secured to the skull with acrylic glue. The experiments began 4-7 days after the operation.. BP was recorded by means of a strain gauge amplifier obtained from Narco Biosystems. HR was measured intervalographically [2]. All parameters were recorded on a Physiograph ink-writing instrument and in some experiments the USCh8-03 automatic writer was used. A fall of BP was induced by intravenous injection of nitroglycerin (3-5 μg/kg), histamine (0.2-0.5 μg/kg), pilocarpine (2-5 μg/kg), or acetylcholine (0.001-0.01 μg/kg). The doses used led to a fall in the mean BP of about 20 mm Hg, without causing any behavioral reactions. All experiments were carried out on animals lying quietly or sleeping. Oxprenolol (Transicor, 2.5 mg/kg) or propranolol (Obsidan, 1-2 mg/kg) was used to block β-adrenoreceptors. To test the effectiveness of the β-adrenoblockade, isoprenaline (Novodrin, 1 μg/kg) was injected. Muscarinic acetylcholine receptors were blocked by Metacin (oxyphenonium bromide, 1 mg/kg). All the drugs were injected intravenously.

EXPERIMENTAL RESULTS

A typical response of BP and the cardiac rhythm to administration of a hypotensive agent is shown in Fig. 1. Blocking sympathetic influences on the heart by the β-blocker Oxprenolol led to a significant decrease in the reflex tachycardia (from 48 to 26 beats/min, respectively). The averaged results are given in Table 1.

It was found in the course of the investigation that the magnitude of the chronotropic response depends on spontaneous fluctuations in the initial HR level: The higher the initial HR the less marked the reflex tachycardia in response to the same fall in BP. Records of two experiments on the same animal on different days are illustrated in Fig. 2. In the first case, when the initial HR was relatively low, it increased by 82 beats/min, but in the second case, when the initial HR was relatively high, the increase was only 62 beats/min. Re-

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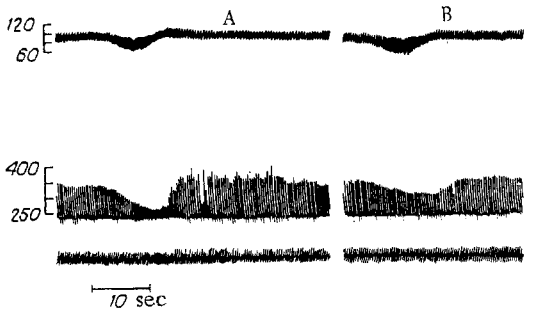

Fig. 1

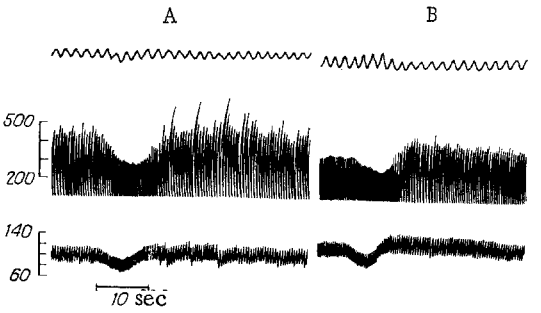

Fig. 2

Fig. 1. Reflex tachycardia in response to lowering of BP pilocarpine (10 μg/kg) in an unanesthetized cat before (A) and after (B) β-adrenoreceptor blockade by Oxprenolol (2.5 mg/kg). Top trace represents BP (in mm Hg), middle trace is intervalogram (R-R).

Fig. 2. Effect of initial heart rate on reflex tachycardia in response to fall of BP. A and B) Responses on different days in the same animal. Top curve — respiratory movements, middle — intervalogram (R-R), bottom — BP (in mm Hg).

TABLE 1. Effect of Pharamacological Agents on BP and HR during Depressor Baroflex (M ± m)

Experimental conditions	No. of animals	Mean BP, mm Hg		HR, beats/min	
		initial value	change	initial value	change
Control	7	94±2,4	—20±0,6	162±6,9	52±7,8
After β-adrenoreceptor blockade:					
by oxprenolol	5	95,5±3,3	—18±0,7	162±2,3	22±3,2
by propranolol	1	106±2,8	—20±1,1	138±1,6	38±1,9
After muscarinic acetylcholine receptor blockade by oxyphenonium bromide	3	106±8,1	—18±1,0	236±26,8	19±2,1

gression analysis of results obtained in 46 tests on seven animals showed a linear relationship, with a negative trend, between the degree of baroreflex tachycardia and the initial HR (Fig. 3). Experiments with limited scatter of the mean BP values (80-120 mm Hg), the pulse pressure (16-35 mm Hg), and the rate of the hypotensive reaction (4-6.6 mm Hg/sec) were used for mathematical analysis, so that the influence of these parameters in determining baroreceptor activity [3] on the relationship studied could be minimized.

It will be clear from Fig. 3 that the same relationship also held good after pharamacological blocking of sympathetic influences on the heart; in this case, however, the graph lies at a significantly lower level, i.e., the magnitude of the tachycardia corresponding to each HR level tested was less than in the control experiments.

Assessment of the relative role of the sympathetic and parasympathetic innervation in the mechanism of baroreflex tachycardia on the basis of these graphs shows that when the initial HR (HR_0) was 140 beats/min the contribution of the two divisions of the nervous system was about equal. With a lower initial HR the relative role of the parasympathetic innervation increased, whereas if the initial HR was higher, the sympathetic division made the more important contribution. For instance, with HR_0 = 175 beats/min the relative contribution of the sympathetic innervation to the baroreflex tachycardia was about 73%.

A similar analysis conducted on the basis of the results obtained with the peripheral muscarinic cholinolytic oxyphenonium bromide (Table 1), if it did not take into account the rule described above, could lead to exaggeration of the role of the parasympathetic innervation, for reflex tachycardia after administration of oxyphenonium was reduced by almost two thirds compared with the control (52 and 19 beats/min, respectively). Oxyphenonium in this case led to a sharp rise in the initial HR.

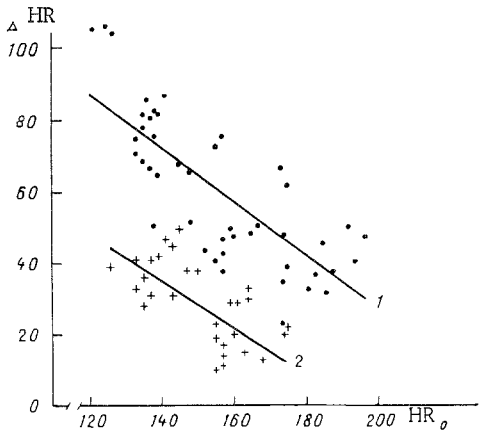

Fig. 3. Reflex tachycardia as a function of initial HR before (1) and after (2) β-adrenoreceptor blockade. Abscissa, HR_0, beats/min; ordinate, reflex tachycardia (ΔHR), beats/min. 1) Regression line: $\Delta HR = 175 - 0.74\ HR_0$, coefficient of correlation −0.77 ($P < 0.001$); 2) regression line: $\Delta HR = 128 - 0.66\ HR_0$, coefficient of correlation −0.68 ($P < 0.001$).

This overestimation could be the reason for the conclusions drawn by the authors cited previously [6, 8], that the parasympathetic innervation plays the dominant role in baroreflex regulation of the heart rate, for their conclusion on the nature of the efferent mechanisms was based on comparison of the results of control experiments, experiments with atropine (which caused a marked rise in HR_0), and experiments with propranolol (which lowered the initial HR). It is also known that atropine-induced tachycardia is complex in nature and that one of its mechanisms is activation of the sympathico-adrenal system [1, 4].

The results of the present investigation are evidence that reflex tachycardia in unanesthetized cats in response to a fall of 20 mm Hg in the mean BP has a mixed mechanism, in agreement with results obtained in similar investigations on waking dogs [10]. The existence of two mechanisms of baroreflex tachycardia makes the strict quantitative assessment of the relative role of the two innervation systems in its production by the pharmacological blockade technique more difficult, for blocking one channel of action on the pacemaker may increase the relative influence of the other channel. Nevertheless, the capacity of each channel can be estimated by this method. As the graphs in Fig. 3 show, the parasympathetic system is limited in its ability to induce reflex tachycardia when the initial HR level is high. This may explain the fact that in experiments whose conditions (vivisection procedures, immobilization of the animals, and so on) provoked an increase in heart rate it was concluded that the sympathetic innervation plays the dominant role in the mechanism of baroreflex tachycardia [5, 9].

This rule — weakening of the reflex chronotropic reaction of the heart with an increase in the initial HR — must also be taken into consideration when the depressor baroreflex is used as a function test in clinical investigations, for changes in heart rate in healthy subjects with a relatively low initial HR are often compared with changes in patients with a relatively high initial HR [7]. The material in this paper shows that when such a comparison is made it is essential to choose a control group of healthy subjects whose initial heart rate does not differ greatly from that of the patients under investigation.

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FREQUENCY FACILITATION IN NEUROMUSCULAR SYNAPSES OF THE FROG SARTORIUS MUSCLE

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KEY WORDS: neuromuscular synapse; frequency facilitation; binomial parameters of mediator liberation.

Frequency facilitation, or an increase in mediator liberation in response to a stepwise change in stimulation frequency from 0.5 to 10 Hz, is one form of facilitation in the neuromuscular junction. It has been suggested that this form of facilitation is based on mobilization of the mediator, i.e., "migration" of quanta of mediator toward the points of liberation, or their preparation for liberation [4, 5, 8, 9]. In this case, in accordance with the statistical hypothesis of mediator liberation [6], the increase in quantum composition of end-plate potentials (m) during frequency facilitation ought to be accompanied by an increase in the reserves of accessible mediator (n) without any change in the probability of liberation of a mediator quantum (P), and this has been demonstrated experimentally [5].

However, determination of the binomial parameters of mediator liberation at relatively low frequencies of stimulation (5-10 Hz) revealed an appreciable increase in the parameter P also [3]. This suggests that frequency facilitation may reflect not only mobilization of the mediator, but also a change in the probability of liberation of a mediator quantum. The investigation described below was carried out to test this hypothesis.

EXPERIMENTAL METHOD

Neuromuscular preparations of the sartorius muscle of *Rana ridibunda* were perfused with Ringer's solution of the following composition (in mM): NaCl 115; KCl 2; $CaCl_2$ 0.9-1.8; $MgCl_2$ 4-6; pH 7.2-7.4. End-plate potentials (EPPs) and miniature EPPs (MEPPs) were recorded intracellularly by a standard microelectrode technique from the synaptic regions of superficial muscle fibers. To investigate frequency facilitation, the motor nerve was stimulated by series of pulses (600 stimuli) at frequencies of 0.5, 2, 4, 6, and 8 Hz. The last 100-200 EPPs were recorded in each series [9]. Assuming an exponential relationship between the evoked liberation of mediator (m) and the frequency of stimulation (f)

$$m = m_0 e^{kf},$$

the coefficient of frequency facilitation (k) and the value of m at zero frequency (m_0) were determined by the method of least squares. The method of determining binomial parameters of mediator liberation was fully described previously [1-3, 5]. Values of facilitation after single and paired (interval 200 msec) stimulation also were determined. The testing pulse was applied 16-600 msec after the conditioning stimulus. The intervals between stimulations were 12-30 sec. The dynamics of facilitation in this case was described by the equation $F_t = F_0 e^{t/\tau}$ [10], where F_t denotes facilitation during time t after conditioning stimulation, F_0 facilitation at t = 0, and τ is the time constant of k of facilitation. Changes in the parameters m, n, and P during facilitation (F_m, F_n, F_p) were calculated by the equations:

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