INCREASE IN VAGAL TONE AND LIMITATION OF CARDIAC ARRHYTHMIAS DURING ADAPTATION TO CONTINUOUS STRESS

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Adaptation to repeated short exposures to stress can limit or prevent arrhythmias associated with acute ischemia, reperfusion, myocardium infarction, and postinfarction cardiosclerosis. An important role in the mechanism of this protective effect is played by activation of opioidergic, GABA-ergic, and serotoninergic central stress-limiting systems [2]. The problem of the role of the parasympathetic innervation in the protective, antiarrhythmic effect of this adaptation still remains unsolved despite evidence that vagal stimulation or an initially high tone of the parasympathetic nervous system may limit [3] or even terminate adrenergic arrhythmias by weakening adrenergic effects on the heart [5].

The aim of this investigation was to assess the dynamics of vagal tone during adaptation to continuous moderately severe immobilization stress and to determine whether the increase in vagal tone observed induces an antiarrhythmic effect in ischemic and reperfusion arrhythmias.

EXPERIMENTAL METHOD

Experiments were carried out on 74 male Wistar rats weighing 180-250 g. In the experiments of series I the animals were divided into four groups: 1) control, 2) exposed to stress for 1 day, 3) to stress for 5 days, 4) to stress for 5 days + atropine. As a model of continuous moderate immobilization stress the rats were kept in special constraining cages which allowed them to take food and water freely. To determine the fibrillation threshold of their heart (FTH) the rats were anesthetized with urethane (1.6 g/kg), artificially ventilated, and thoractomy was performed, after which the heart was stimulated by premature single square pulses, 10 msec in duration, by means of an SEN 3201 stimulator (Nihon Kohden, Japan), triggered by the R wave of the ECG, through a coaxial needle electrode, inserted into the myocardium at the apex of the left ventricle. The beginning of the relative refractory period, i.e., the time when a single response appeared to stimulation, was determined during scanning of the ST interval with pulses of 3 times the threshold strength. The fibrillation threshold of the ventricles was determined as the weakest current in milliamperes during which fibrillation developed. Atropine sulfate was injected subcutaneously 3 times a day in a dose of 10 mg/kg for 2 days before the rest period of stress, so that cholinergic influences on the heart could be excluded sufficiently completely [1]. In series II, experiments were carried out with transient ischemia and reperfusion of the heart in animals divided into the following groups: 1) control, 2) control + atropine, 3) stress for 5 days, 4) stress for 5 days + atropine. Under urethane anesthesia and with thoracotomy and artificial ventilation the ECG was recorded in standard leads on a Mingograf-34 apparatus. A ligature was placed under the left coronary artery to constrict the artery, and after ischemia for 10 min the ligature was released and the response of the heart to reperfusion and reoxygenation estimated for 5 min. The results were subjected to statistical analysis by Student's test.

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TABLE 1. HR and FTH of Rats during Adaptation of Continuous 5-Day Stress and Blocking of Cholinergic Innervation (experiments of series I)

Group of animals	HR, beats/min	Ventricular fibrillation threshold, mA
1- (n=10)	441±8	7,84±0,24
2- (n=10)	413±20	4,10±0,57*
3- (n=7)	354±11*	7,64±0,58
4- (n=8)	492±13*,***	5,07±0,62*,**

Legend. *$p < 0.001$ compared with group 1; **) $p < 0.01$, ***) $p < 0.001$ compared with group 3.

TABLE 2. Effect of 5-Day Stress on Cardiac Arrhythmias Associated with Ischemia and Reperfusion, with Intact and Blocked Cholinergic Innervation (series II)

Parameter	Ischemia for 10 min				Reperfusion for 5 min			
	group of animals							
	(n=11) 1	(n=11) 2	(n=8) 3	(n=9) 4	(n=11) 1	(n=11) 2	(n=8) 3	(n=9) 4
Extrasystoles (ES):								
Number of animals with ES	11	11	8	9	10	11	8	8
Total number of ES per group	324	421	178	737	219	305	70	204
Mean number of ES per animal	29,4±7,0	38,3±9,6	22,0±9,9	82±37	19,9±6,8	27,7±9,6	8,0±2,8	22,7±11,0
Ventricular tachycardia (VT)								
Number of animals with VT	6	6	2	5	10	10	6	7
Total duration per group, sec	29,2	62,9	4,0	55,2	202	148	64	118
Average duration per animal, sec	2,7±0,9	5,7±2,3	0,5±0,32*	6,1±2,5***	18,4±4,1	13,4±4,2	7,6±2,4*	13,1±5,2
Ventricular fibrillation (VF):								
Number of animals with VF	2	2	0	2	3	3	0	2
Total duration per group, sec	11,1	12,6		7	45,1	78,4		18,4
Average duration per animal, sec	1,0±0,7	1,1±0,8		0,8±0,57	4,1±3,0	7,1±6,9		2,04±1,4
Total duration of severe forms of arrhythmia (VT + VF):								
Per group, sec	41,0	75,5	5	62,2	247	232	64	137
Per animal, sec	3,7±1,5	6,9±2,9	0,5±0,32*	6,9±2,9***	22,5±5,1	21,1±10,3	7,6±2,4**	15,2±5,3

Legend. *$p < 0.05$, **$p < 0.01$ compared with group 1; ***$p < 0.05$ compared with group 3.

EXPERIMENTAL RESULTS

The heart rate (HR) and ventricular fibrillation threshold are shown in Table 1. Clearly 24 h after the rats were kept under conditions of stress no significant changes had taken place in HR, but the fibrillation threshold was reduced by half; by the 5th day marked bradycardia developed (HR fell by 87 beats/min) and the fibrillation threshold level was restored at the same time to the control value. Injection of atropine under these conditions led to restoration of HR and to lowering of FTH.

Adaptation to continuous, moderately severe immobilization stress for 5 days thus leads to an increase in vagal tone, and the bradycardia which develops is accompanied by restoration of FTH, when initially depressed in response to the action of stress.

The results of the experiments of series II are given in Table 2. They show that the main parameter characterizing the severity of arrhythmias, namely the total duration of ventricular tachycardia and fibrillation of the heart, could be clearly determined in the control animals actually during ischemia, and it increased sixfold during subsequent reperfusion. After adaptation to a 5-day period of stress, dangerous ischemic arrhythmias almost completely disappeared, and the duration of reperfusion arrhythmias was reduced threefold. Injection of atropine into the adapted animals sharply reduced this powerful protective antiarrhythmias effect of adaptation and it ceased to be significant. Consequently, the increase in vagal tone during adaptation to continuous stress undoubtedly plays an important role in the antiarrhythmic effect of adaptation in ischemic and reperfusion-induced heart damage. Similar results in relation to tonic excitation of antinociceptive centers were obtained previously [6]. Essentially in such cases we have a situation in which tonic excitation of particular brain centers maintains a defensive response of importance to the body as a whole.

When this concrete fact is discussed, the important role of adrenergic effects in the mechanisms of ischemic and reperfusion arrhythmias must be remembered [8, 10]. An increase in vagal tone limits adrenergic influences on account of the inhibition of noradrenalin release from sympathetic terminals by acetylcholine [7], and also significant limitation of the response to noradrenalin at the receptor level [11]. It must also be recalled that muscarinic acetylcholine receptors in the heart are connected through guanyl-nucleotide-dependent G-proteins with K^+-channels, and also with adenylate cyclase, linked with β-receptors. Through muscarinic receptors acetylcholine activates K^+-channels and increases the K^+ current from the cell, but inhibits adenylate cyclase, thus limiting *c*AMP-dependent entry of Ca^{2+} into the cell. As a result of both these mechanisms hyperpolarization develops and cardiomyocyte excitability falls [4, 9].

If the above results are judged on the basis of the principle of "limitation" of the stress-limiting systems of the body [2], the role of the parasympathetic regulation of the heart, demonstrated above, in the mechanism of the antiarrhythmic action of adaptation to stress must be accepted as demanding an urgent search for new cardioprotective agents which would possess to the full the adrenolytic action of acetylcholine, but would be free from the excessive negative chronotropic and inotropic effects of that drug, and would thus be optimal arrhythmics.

LITERATURE CITED

1. V. M. Kontsevoi, "Effect of some vegetotropic poisons on the intensity of cell reproduction," Author's Abstract of Candidate's Dissertation, Medical Sciences, Vitebsk (1971).
2. F. Z. Meerson and M. G. Pshennikova, Adaptation to Stress Situations and Physical Exercise [in Russian], Moscow (1988).
3. K. V. Sudakov, E. A. Yumatov, and L. S. Ul'yaninskii, Mechanisms of Development of Stress [in Russian], Kishinev (1987), pp. 52-79.
4. G. E. Breitwieser and G. Szabo, Nature, **317**, 538 (1985).
5. K. M. Kent, E. R. Smith, D. R. Redwood, and S. E. Epstein, Circulation, **47**, 291 (1973).
6. G. N. Kryzhanovskii (G. N. Kryzhanovsky), Central Nervous System Pathology: A New Approach, New York (1986), p. 421.
7. M. N. Levy and B. Blattberg, Circulat. Res., **38**, 81 (1976).
8. B. Lown and R. Verrier, New Engl. J. Med., **294**, 1165 (1976).
9. E. J. Neer and D. E. Clapham, Nature, **333**, 129 (1988).
10. J. E. Skinner, Stress and Heart Disease, R. E. Beamish et al. (eds.), Boston (1985), pp. 44-59.
11. R. L. Verrier, Circulation, **76**, Suppl. 1, 1-48 (1987).