Protective Effect of Neurotensin during Vagal Arrhythmias

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The effects of neurotensin and its analog [D-Trp[11]]-neurotensin were studied on Wenckebach arrhythmia and atrioventricular dissociation provoked by vagal volley stimulation. In both cases the antiarrhythmic effect of neurotensin was observed, which was mediated by activation of cardiac β-adrenoreceptors and manifested 40-60 sec after its administration. The neurotensin analog had no cardioprotective activity, but when applied before neurotensin, it demonstrated antagonism to the protective effect of natural neurotensin.

Key Words: *neurotensin; Wenckebach arrhythmia; atrioventricular dissociation*

Regulator peptides actively participate in the control of cardiac activity. Neurotensin, a peptide consisting of 13 amino acids, increases heart rate (HR) [5,7,8], augments myocardial contractility [12], and changes the character of parasympathetic regulation of cardiac rhythm [5]. The present work studies the effects of neurotensin during arrhythmias provoked by stimulation of the vagus nerve (VN). We used the model of a second-degree atrioventricular (AV) block (Wenckebach type) and AV-dissociation [3,4].

MATERIALS AND METHODS

The study was carried out on 29 random-bred adult cats (body weight 2.5-3.5 kg) under intraperitoneal anesthesia with a mixture of chloralose (75 mg/kg) and Nembutal (15 mg/kg) and artificial ventilation. Both VN were cut at the cervical level, and the peripheral end of one of them was stimulated by volleys of 6 or 9 rectangular voltage pulses. As the left VN produces a more pronounced effect on AV-conduction, and the right VN affects predominantly cardiac automatism [6], we stimulated the left VN to provoke Wenckebach arrhythmia, and the right VN to induce AV-dissociation. Impulse duration and frequency in a train were, respectively, 2 msec and 40 Hz, their amplitude being 5 to 6 threshold value. An electrogram of the right atrium was recorded with a unipolar probe inserted through the femoral vein. Neurotensin (Boehringer Mannheim) and its analog [D-Trp[11]]-neurotensin (Sigma) were administered intravenously in streams together with 0.5 ml physiological saline. The doses of neurotensin and its analog were, respectively, 3.0×10^{-8} M (0.05 mg) and 2.35×10^{-8} M (0.04 mg). The doses were chosen according to [5], who showed that neurotensin in this concentration has a pronounced cardiotropic activity, manifested in HR increase and in changes of functional structure of vagal influence on cardiac rhythm. In control experiments, 0.5 ml peptide-free physiological saline was administered during arrhythmia. In several series of experiments the peptide analog was applied 5-10 min before neurotensin; a similar time interval was also used in preliminary administration of the β-blocker obsidan (1 mg/kg intravenously). The results were statistically analyzed [2].

RESULTS

Duration of cardiac cycle in vagotomized cats was 325.4±12.1 msec, and duration of the *PR* interval was 74.4±6.6 msec. Vagal stimulation decreased HR and synchronized heart beats to volley rhythm. The

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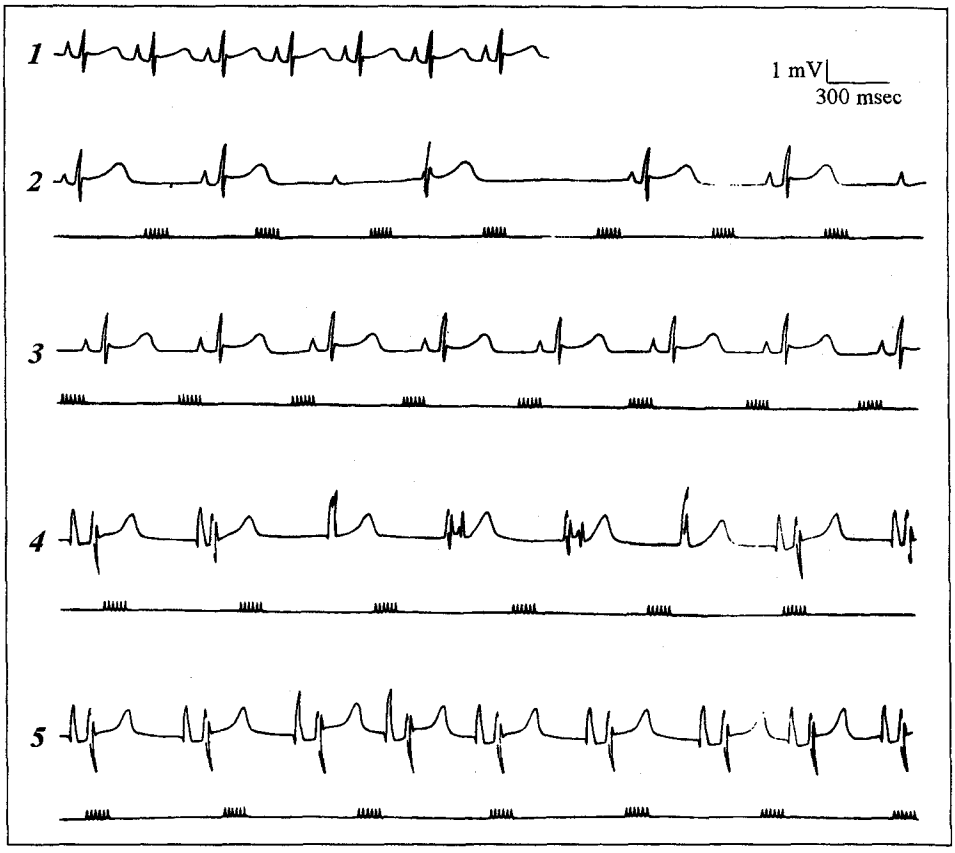

Fig. 1. Effects of neurotensin on Wenckebach arrhythmia and atrioventricular (AV) dissociation by volley stimulation of vagus nerve. *1*) initial cardiac rhythm in vagotomized cat; *2*) Wenckebach arrhythmia with 3:2 AV-conduction. Pause after conduction block of atrial impulse is interrupted by nodal escape (the third *QRS* complex); *3*) restoration of synchronization between vagal and cardiac rhythms after administration of neurotensin; *4*) isorhythmic AV-dissociation; *5*) sinus arrhythmia which arose after neurotensin administration. In *2-5* panels the upper curve is atrial electrogram and the lower curve is the artifact of vagal stimulation.

latter phenomenon made it possible to affect the cardiac rhythm to a certain extent by varying the frequency of vagal volleys. The upper and lower boundaries of the controlled variations of cardiac cycle duration by 6-pulse vagal stimulation were 580.3±13.4 and 725.2±14.2 msec, and by 9-pulse stimulation — 620.7±10.1 and 795.2±12.9 msec, respectively. A decrease in the intervolley period by 20-30 msec in comparison with its duration at the upper range boundary of controlled bradycardia impaired synchronization of vagal and cardiac rhythms and led to a second-degree AV block (Wenckebach type, Fig. 1). The characteristic feature of this arrhythmia was varying position of the vagal stimulus in the series of cardiac cycles, which was manifested as a persistent decrease in the interval between *P* peak and the following vagal volley (*P*—stimulus interval). This resulted in periodically repeated changes of the *PP* and *PR* intervals, manifested as Wenckebach arrhythmia. Upon a 9-pulse vagal stimulation, a decrease in *P*—stimulus interval from 520.4±15.3 to 460.5±11.5 msec increased the *PR* interval from 92.5±7.6 to 140.3±9.4 msec; on the contrary, duration of cardiac cycle decreased at the same time from 725.3±16.1 to 615.1±13.6 msec. A decrease in the *P*—stimulus interval to 440.3±10.9 msec resulted in complete conduction block of the next atrial impulse, thereafter periodicity repeated itself. Neurotensin arrested arrhythmia (n=7) and restored synchronization between vagal and cardiac rhythms (Fig. 1). The latent period of this effect was 40.7±4.6 sec. Under synchronization, the frequency of vagal volley and cardiac rhythm strictly corresponded to each other, which was reflected in a stable position of vagal stimulus in the serial cardiac cycles and in a constant value of the *P*—stimulus interval (460.2±12.7 msec). The latter determined the correct rhythm of cardiac beats with duration of *PP* and *PR* intervals of 580.3±12.6 and 100.4±9.8 msec, respectively.

The ability of the heart to synchronize the rhythm of its beats with the frequency of vagal volleys was used to induce AV-dissociation. This form of arrhythmia is manifested in a simultaneous activity of two pacemakers: sinoatrial, which provides atrial

excitation, and atrioventricular, which determines ventricular depolarization [1]. Under synchronization of vagal and cardiac rhythms, HR was decreased to the level of AV-nodal automatism by increasing the intervolley duration. The slowing down of cardiac rhythm below 71.3±6.8 beats/min was accompanied by the appearance of regular nodal escape and development of arrhythmia (n=7). By isorhythmic dissociation (Fig. 1) against the background of 6-pulse vagal stimulation, ventricular excitation was performed in the correct rhythm with an interval of 590.7±13.4 msec; at the same time duration of atrial cycle changed from 450.8±12.7 to 650.7±14.1 msec depending on the position of vagal stimulus relative to the cardiac cycle. Administration of neurotensin resulted in restoration of sequential activation of atria and ventriculi by impulses from the sinus node. In 58.7±10.3 sec after administration of the peptide, there was an arrest of AV-dissociation and appearance of sinus arrhythmia with cardiac cycle duration varying from 440.5±11.1 to 560.3±13.4 msec.

The protective effect of neurotensin on Wenckebach arrhythmia and AV-dissociation was prevented by preliminary block of β-adrenoreceptors by obsidan (n=5). The neurotensin analog differing from natural peptide by substitution of tyrosine in 11th position by D-tryptophan ([D-Trp^{11}]-neurotensin) had no antiarrhythmic activity (n=5), but demonstrated antagonism relative to subsequent effect of neurotensin (n=5). The latter is consistent with the observation that modification of neurotensin molecule in position 10-13 leads to a drastic decrease in its activity, although it does not notably modify its affinity for receptors [11,12]. Interactions with the receptors lead to a marked and prolong tachyphylaxis in response to natural neurotensin [5,7], which is manifested by the lack of its activity upon repeated administration.

Previously, we showed that administration of neurotensin to cats leads to a short-term tachycardia mediated via activation of cardiac β-adrenoreceptors and is comparable by a number of parameters to the dynamics of positive chronotropic effect of epinephrine [5]. The positive chronotropism of neurotensin is shown in present study to be a necessary component of its protective properties in vagal arrhythmias. In addition to acceleration of cardiac rhythm by Wenckebach arrhythmia, neurotensin restored synchronization of vagal and cardiac rhythms in the conditions of increased rate of vagal volleys, which initially were not followed by cardiac beats and had an arrhythmogenic effect. Neurotensin restored the sinus node automatism, which was reduced in the conditions of AV-dissociation, and arrested arrhythmia. A characteristic feature of the considered effects of neurotensin is the latency of 40-60 sec, which is larger than the latency (20-30 sec) of neurotensin effects on cardiac rhythm under initial conditions. Bearing in mind that one of the mechanisms of neurotensin chronotropic effect is mediated via endogenous catecholamines [5,7], this mismatch can be explained by elimination of the peptide effect under vagal stimulation due to inhibitory action of acetylcholine on secretion of norepinephrine from sympathetic terminals due to activation of presynaptic M-cholinoreceptors [9]. Another cause of longer latency of neurotensin action can be the necessity to correct not only reduced automatism, but also delayed AV-conduction.

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