Cardiotropic Effects of Somatostatin and Its Antagonists

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Somatostatin reduces cardiac rhythm in cats, the effect being abolished by the M-cholinolytic methacin, the ganglioblocker benzohexonium, or somatostatin antagonist. Somatostatin suppresses vagal chronotropic effect by reducing its tonic component, while the synchronizing vagal component increases. The antagonist of somatostatin exerts an opposite effect: it eliminates the influence of somatostatin on the tonic vagal component and reverses its effect on the synchronizing component.

Key Words: *somatostatin; somatostatin antagonist; vagus; cardiac rhythm*

There is considerable evidence indicating that somatostatin (SS) modulates cardiac activity. Somatostatin slows down the heart beat [10,15], elicits a negative inotropic effect [7], and decreases myocardial conductivity [6,15]. It was interesting to compare cardiotropic effects of SS with the effects of SS peptide antagonist. In the present study we examined the effects of these compounds on heart rate (HR) and parasympathetic regulation of heart rhythm in cats.

MATERIALS AND METHODS

Experiments were performed on 42 cats weighing 2.5-3.5 kg. The animals were anesthetized with chloralose (75 mg/kg) and Nembutal (15 mg/kg) and transferred to artificial ventilation. Both preparations were injected intraperitoneally. The peripheral end of the right vagus was stimulated by bursts of 3, 6, or 9 rectangular pulses (2 msec, 40 Hz) with an amplitude of 5-6 thresholds. A unipolar probe was inserted into the right atrium via femoral vein for enhanced ECG recording. The *P* wave indicated the beginning of the intervalogram for SS (Sigma). The SS antagonist (7-amino-heptanoyl-Phe-D-Trp-Lys-Thr[Bzl]) was infused intravenously in 0.5 ml normal saline. The results obtained were statistically processed by the method of direct differences [1].

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RESULTS

In the first series of experiments (n=7) we studied the effect of SS (1.3×10^{-8} M) on HR. This peptide reduced HR from 195.6±5.2 to 180.5±4.4 beats/min, i.e., by 7.7% ($p<0.05$), the latency of the effect being 23.6±3.5 sec. The maximum length of cardiac cycle was observed 45.7±4.6 sec after the onset of chronotropic reaction. Bradycardia was preserved for 6-15 min after administration of the peptide. Repeated administrations of SS induced no tachyphylaxis. The effect of SS was abolished by pretreatment with the M-cholinolytic methacin (0.0025 mg/kg), the ganglioblocker benzohexonium (8 mg/kg), or SS antagonist (2.6×10^{-8} M). The SS antagonist (n=10) had no effect on HR.

In the second series of experiments we investigated the influence of SS on the dynamics of vagal chronotropic effect (VCE) induced by pulse stimulation of the vagus. In established vagal bradycardia cardiac contractions were synchronous with the rhythm of vagal stimulation. For example, with an initial HR of 194.3±4.5 beats/min a 6-pulse stimulation of the vagus led to synchronization of vagal and cardiac rhythms which lasted from 103.5±3.4 to 84.6±4.3

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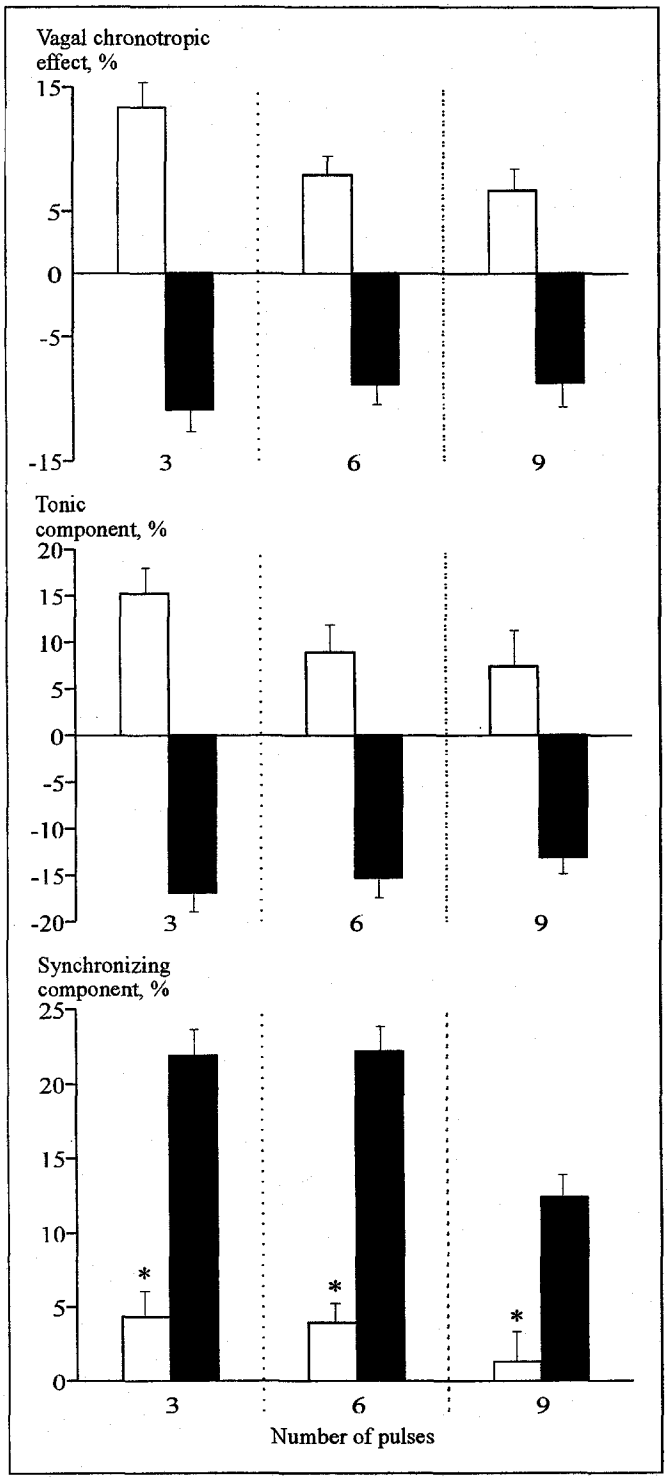

Fig. 1. Effect of somatostatin and its antagonist on vagal chronotropic effect and its components. Changes are plotted as percent of the initial values which is taken as zero. White bars: effect of antagonist; black bars: effect of somatostatin. Statistically insignificant differences are indicated with an asterisk.

beats/min (the upper and lower limits of synchronization, respectively). The width of the synchronization range reflected the magnitude of the synchronizing component, while the level of bradycardia, upon which synchronization had developed, reflected the magnitude of the tonic vagal component. The tonic component was calculated as the difference between the initial HR and the upper limit of synchronization. The magnitude of VCE was calculated as the sum of tonic and synchronizing components. Somatostatin suppressed VCE (n=11, Fig. 1). Stimulation of the vagus with 3-, 6-, and 9-pulse bursts reduced VCE by in 10.9, 8.8, and 8.7% (p<0.02). The components of VCE were changed in a different manner. For example, the tonic component decreased by 16.9, 15.3 and 13.1%, respectively (p<0.02), compared with the initial level, while the synchronizing component increased, respectively, by 21.9, 22.2 and 12.4% (p<0.05).

In the third series (n=7), the vagotropic effect of SS antagonist was studied. This compound produced an opposite effect on parasympathetic regulation of heart in comparison with the effect of SS (Fig. 1). After administration of SS antagonist, VCE increased by 13.3, 7.9, and 6.7% (p<0.05), respectively, upon stimulation with 3-, 6- and 9-pulse bursts. This effect was provided by an increase in the tonic component by 15.2, 8.9, and 8.2% (p<0.05), respectively. The magnitude of synchronizing vagal influences did not change. The effect of SS antagonist was observed for at least 30 min after its administration.

In the fourth series (n=7), the effect of SS on vagal regulation of heart was examined after administration of SS antagonist. The antagonist abolished the inhibiting effect of SS on VCE and its tonic component. Under these conditions SS decreased the synchronizing component, i.e., exerted an opposite effect on it compared with the effect observed without the antagonist. Upon 3-, 6- and 9-pulse stimulation of the vagus, the synchronizing component decreased, respectively, by 13.2, 10.8, and 15.5% (p<0.02).

The ability of SS to slow down HR in cats is consistent with the data obtained in other animal species. It was demonstrated that the peptide reduces HR in guinea pigs [6], rats [10], and amphibia [7]. A decrease in the sinus automatism was observed in humans in clinical practice [15] and in experiments with isolated human atrial fibers [12]. Blockade of cardiac M-cholinergic receptors does not abolish the effect of SS on isolated heart of the toad *Bufo marinus* [7]; in other animals, the effect is atropine-dependent. This holds true for cats. Presumably, this dependence results from stimulation of acetylcholine release from parasympathetic cardiac neurons by SS [16].

For analysis of cardiotropic effects of SS we used a short cyclic SS analog acting as a competitive antagonist toward the secretion of growth hormone, insulin, and glucagon [9]. This antagonist abolishes

the SS-mediated hemodynamic reactions [13]. Elimination of chronotropic effect of SS in cats by the antagonist implies that the effect of the peptide on HR is mediated by specific receptors located on cholinergic neurons in the intramural cardiac ganglia or on the peripheral endings of the vagus, which leads to secretion of acetylcholine that decelerates HR. This scheme accounts for the relationship between the dependence of chronotropic effect of SS on M-cholinolytics and ganglioblockers.

It was demonstrated that SS is colocalized with acetylcholine in parasympathetic cardiac neurons and can be released upon stimulation of the vagus [7]. Therefore, it was interesting to examine the cholinergic chronotropic effect of SS. In cats, SS decreased this effect, which is associated with several mechanisms. It was reported that the inhibiting effect of the vagus is regulated in accordance with the initial automatism of the heart [5]. The interventions (including the pharmacological ones) that increase the initial HR promote the inhibiting effect of the vagus, while a decrease in HR leads to an opposite effect. Previously, we observed a decrease in VCE after administration of taurine or pilocarpine (compounds that decelerate HR) [3,4] and an increase in this effect after administration of epinephrine, serotonin, or neurotensin (compounds that accelerate HR) [2,3]. Thus, suppression of VCE and its tonic component caused by SS is probably associated with deceleration of initial HR. Another mechanism may be related to the effect of the peptide on electrophysiological properties of the myocardium. Is was reported that the effect of SS on the heart is realized via an increase in potassium conductivity [8]. This may render the membrane potential of the pacemaker close to the equilibrium potassium potential, thus decreasing the electromotive force for potassium ions. Therefore, potassium outflow caused by acetylcholine released from the vagus terminals decreases, which diminishes VCE. Desensitization of M-cholinergic receptors associated with the stimulation of basal release of acetylcholine in the atria by SS [16] may also inhibit VCE.

Somatostatin induces contralateral changes in the VCE components: the tonic component decreases, while the synchronizing component that determines the ranges of the synchronization of vagal and cardiac rhythms increases. The opposite modulation is probably associated with the fact that the above-mentioned vagal influences are realized via different mechanisms. For example, the decelerating tonic effect is provided by an increase in potassium conductivity and a decrease in the rate of slow diastolic depolarization of the pacemaker cells [14], while the synchronizing effect is based on a short-term hyperpolarization of the sinoatrial node cells which declines during 1-2 cardiac cycles [11]. Different dynamics of vagal components have been observed when SS was administered against the background of its antagonist: the SS-induced decrease in the tonic component is abolished, while the synchronizing component is suppressed. From this observation it can be concluded that both components of VCE are regulated through specific receptors; however, it should be noted that the synchronization component can be modulated via a nonreceptor mechanism with an opposite functional significance.

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