Mechanism of Vagotropic Effect of Somatostatin

O. E. Osadchii, V. M. Pokrovskii, and M. A. Matsko

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 124, No. 10, pp. 372-376, October, 1997
Original article submitted August 27, 1996

Burst stimulation of the vagus nerve in cats results in synchronization of vagal and cardiac rhythms, while their desynchronization leads to sinus arrhythmia. Using a coefficient characterizing the magnitude of chronotropic effect, we have determined a zone of cardiocycle where the stimulating effect of the vagus stimulus was several times higher than in other zones. Somatostatin reduces this zone and increases the range of the *P—P* interval fluctuations in it, while somatostatin antagonist has an opposite effects. The observed phenomenon can underlie the potentiating effect of somatostatin on the dynamics of controlled vagal bradycardia.

Key Words: *vagus nerve; cardiac rhythm; sinus arrhythmia; somatostatin; somatostatin antagonist*

Effect of vagus stimulation depends on the cardiocycle (CC) phase when stimulating pulses are delivered to the vagus nerve (VN), and within a range restricted by a minimally and maximally possible lengthening of the CC cardiac contractions become synchronous with the rhythm of stimulating bursts delivered to the VN. Each vagus burst induces single cardiac contraction, thus allowing one to control heart rate (HR) though modulation of the repetition rate of the bursts [2,6]. This phenomenon is not mediated solely by cholinergic mechanisms [8]. Extension of the synchronization range after somatostatin injection has been previously observed [3]. The present study explores the mechanisms underlying this phenomenon. To this end, vagus-dependent sinus arrhythmia was used as the initial model, since this arrhythmia is analogous to controlled synchronization in terms of the underlying mechanisms [4].

MATERIALS AND METHODS

Experiments were carried out on 32 mature mongrel cats weighing 2.5-3.5 kg. The animals were narcotized with a Chloralose-Nembutal mixture (75 and 15 mg/kg, respectively) and artificially ventilated. The right vagus nerve was divided in the neck near the thyroid cartilage, and bursts consisting of 6 square supramaximal pulses were delivered to its peripheral end. The duration and frequency of the pulses in the burst were 2 msec and 40 Hz, respectively; the amplitude was 5-6 threshold values. The intra-atrial ECG was recorded via a unipolar probe inserted into the right atrium through the femoral vein. The *P* wave of the ECG starts the recording of intervalogram of the heartbeats, which enabled us to determine the phase duration of the cardiac cycle. Somatostatin (Sigma) and its antagonist cyclo(7-aminoheptanoyl-Phe-D-Trp-Lys-Thr[Bzl]) were infused intravenously in 0.5 ml physiological saline. The data were processed statistically using the method of direct differences [1].

RESULTS

The initial HR in unilaterally vagotomized cats was 191.3±5.2 beats/min. Stimulation of VN caused bradycardia accompanied by synchronization of vagal and cardiac rhythms (Fig. 1), which persisted at interburst intervals varying from 532.3±9.8 to 676±10.1 msec. The latter allows reduction in HR from 112.7±4.8 to 88.7±4.9 beats/min (the upper and lower bound-

Department of Normal Physiology, Kuban Medical Academy, Krasnodar

0007-4888/97/0010-0948$18.00

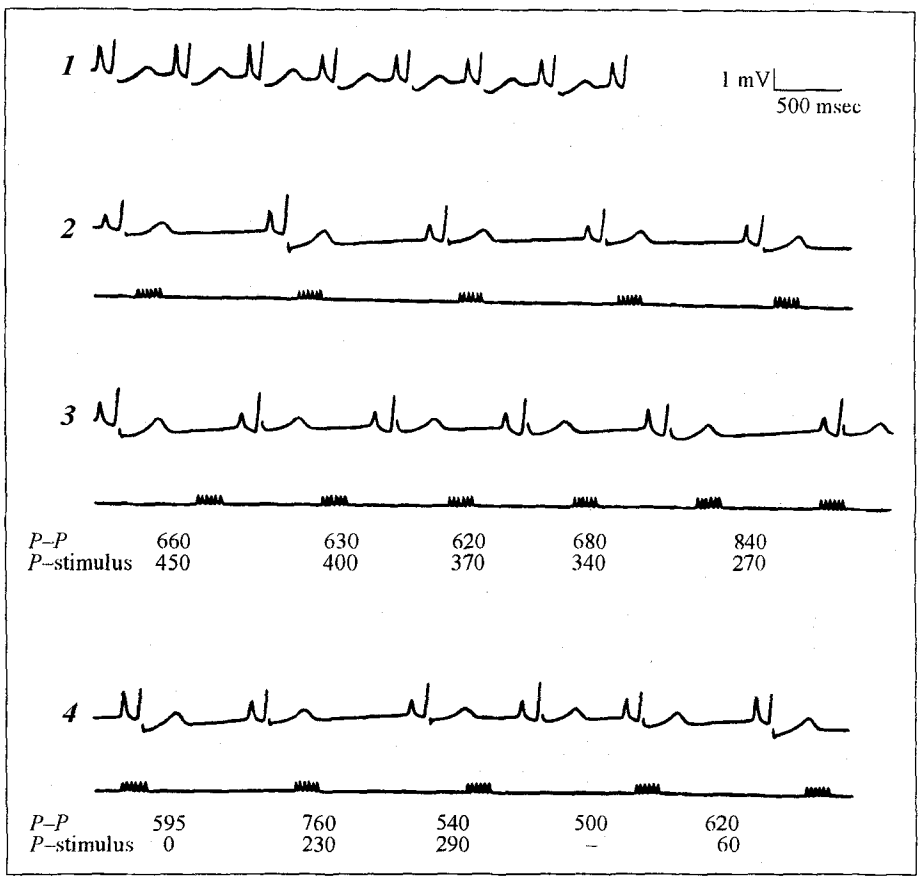

Fig. 1. Dynamics of vagal influence on the cardiac rhythm in burst stimulation of the vagus nerve. Initial cardiac rhythm (*1*); synchronization of the vagal and cardiac rhythms (*2*); sinus arrhythmia above upper (*3*) and below lower (*4*) boundaries of synchronization. Upper and lower records are intra-atrial ECG and artifact from stimulation of vagus nerve, respectively. In fragments *3* and *4* duration of *P—P* interval for each cardiocycle and *P* wave—stimulus interval (between *P* wave and subsequent vagus burst, *P*—stimulus) are shown under the records. *K* coefficient in zones of moderate and pronounced chronotropic effect was 0.5 (660-620/450-370) and 2.3 (680-840/340-270), respectively, in fragment *3*, and 0.7 (595-760/0-230) and 3.7 (760-540/230-290) in fragment *4*.

ary of the synchronization interval, respectively). Under these conditions, bursts were delivered to the VN with a constant delay after *P* wave (interval *P*—stimulus), therefore, the duration of *P—P* intervals was the same in all CC. Stimulation of the VN below or above the synchronization interval results in sinus arrhythmia. Under these conditions the position of the vagal stimulus within the CC varied from cycle to cycle (different *P* wave—stimulus intervals, Fig. 1). The minimal and maximum durations of CC were 536.4±10.7 and 761.4±12.5 msec, respectively, in upper-synchronization arrhythmia, and 435.6±9.9 and 637.8±11.3 msec, respectively, in arrhythmia below the lower limit of synchronization. Since the duration of CC in arrhythmia depended on changes in the *P* wave—stimulus interval, in evaluation of the vagal chronotropic effect we used a coefficient reflecting the relationship between the shift of vagal stimulus within CC and the duration of CC: $K=\Delta P—P/\Delta P—st$, where $\Delta P—P$ is the difference between the minimal and maximum *P—P* intervals and $\Delta P—st$ is the difference between *P* wave—stimulus intervals in the longest and shortest CC. Applying this method, we have found a variation in the magnitude of vagal chronotropic effect within CC. For instance, in arrhythmia above the upper boundary of synchronization interval, the shortening of the *P* wave—stimulus interval from 466.0±10.1 to 344.0±9.5 msec reduced the duration of the *P—P* intervals from 605.0±11.3 to 537.4±10.7 msec ($p<0.001$), which corresponded to $K=0.55\pm0.03$. Further decrease in the *P* wave—stimulus interval led to a sharp lengthening of CC (Fig. 1), accompanied by a 5-10-fold rise in the coefficient characterizing the magnitude of vagal chronotropic effect. For instance, a decrease in the *P* wave—stimulus interval from 344.0±9.5 to 253.0±9.6 msec markedly lengthened the *P—P* interval from 536.5±11.2 to 766.5±13.1 msec ($p<0.001$), which corresponded to $K=2.5\pm0.08$. These changes in the magnitude of vagal chronotropic effect were also seen in arrhythmias below the lower limit of synchronization interval (Fig. 1). This arrhythmia was charac-

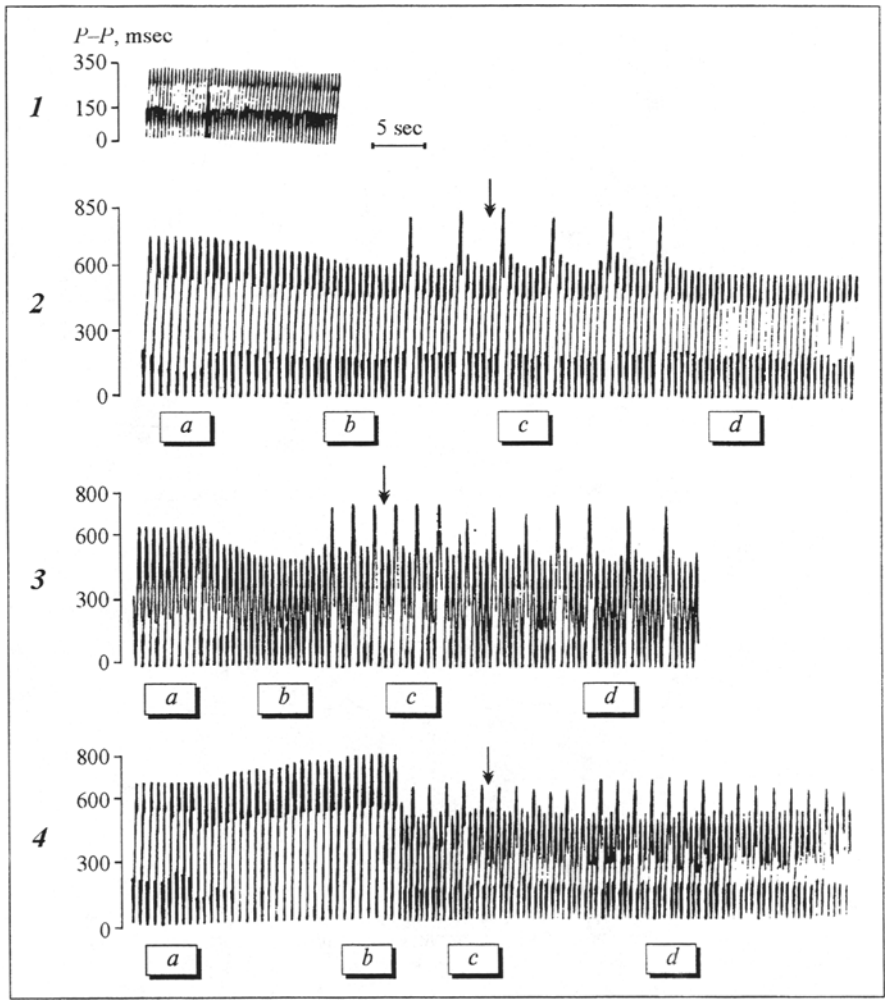

Fig. 2. Effect of somatostatin on intervalogram of heart contraction under conditions of vagus sinus arrhythmia. Primary intervalogram of heart contractions (*1*), effect of peptide in arrhythmia above upper (*2*, *3*) and below lower (*4*) boundaries of synchronization. Arrows indicate the moment of injection; *a*, *b*: boundaries of synchronization of vagal and cardiac rhythms; *c*: sinus arrhythmia, *d*: restoration of regular rhythm due to synchronization of vagal and cardiac rhythms (*2*) or increased amplitude of *P*—*P* interval fluctuations (*3*, *4*) after injection of somatostatin. A fragment of intervalogram between *a* and *b* shows changes in cardiocycle duration under conditions of heart rate control within synchronization interval.

terized by a higher K coefficient (0.78±0.05) in the zone of moderate chronotropic effect. On the basis of these data we isolated 2 zones within CC characterized by different susceptibility to vagal stimulation: zones of moderate ($K<1$) and pronounced (a manyfold increase of K coefficient) chronotropic effect. The latter in all types of arrhythmia coincided with the end of the T wave and lasted 90.9±5.8 msec.

Injection of somatostatin (1.3×10^{-8} M, $n=11$) in arrhythmia above the upper boundary of synchronization in 4 experiments restored synchronization of the vagal and cardiac rhythms. This results in a regular cardiac rhythm (Fig. 2) with CC and P wave—stimulus intervals of 490.1±11.2 and 327.5±9.8 msec, respectively. In most experiments, somatostatin aggravated arrhythmia (Fig. 2), the differences between the minimal and maximum CC increased from 225.2± 12.3 to 271.2±12.6 msec ($p<0.01$), i.e., by 20.4% in comparison with the control. Somatostatin unequally increased the coefficient of the vagal chronotropic effect in different CC zones (Fig. 3): somatostatin had little effect on this coefficient in the zone of moderate chronotropic effect and increased it in the zone of pronounced effect. For instance, in upper-synchronization arrhythmia K rose from 2.5±0.08 to 4.23±0.1 ($p<0.02$) due to reduced length of this zone and increased amplitude of the P—P interval fluctuations. For instance, the zone of pronounced chronotropic effect shrank from 90.9±5.8 to 64.3±5.7 msec ($p<0.02$), while the ΔP—P in this zone increased from 230.0±12.7 to 271.9±13.1 msec ($p<0.05$) in response to somatostatin. Analogous changes were also observed in arrhythmia below the lower boundary of synchronization ($n=11$). Injection of somato-

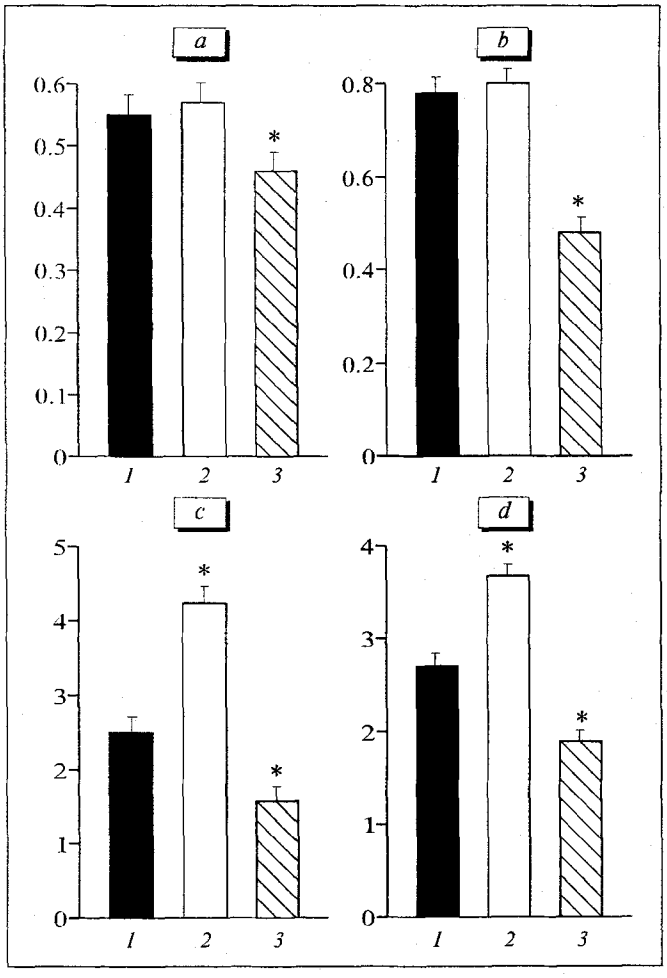

Fig. 3. Effect of somatostatin and its antagonist on the coefficient of vagal chronotropic effect. Ordinate: coefficient of vagal chronotropic effect calculated as the ratio of difference between longest and shortest cardiocycle (ΔP—P) to the difference between longest and shortest P—stimulus interval. *a*, *b*: coefficient in sinus arrhythmia above upper boundary of synchronization of vagal and cardiac cycles; *c*, *d*: coefficient in sinus arrhythmia below lower boundary of synchronization. Dynamics of the coefficient in the zone of moderate (*a*, *c*) and pronounced (*b*, *d*) chronotropic effect. *1*) initial coefficient; *2*) after injection of somatostatin; *3*) after injection of somatostatin antagonist. *$p<0.05$ compared with *1*.

statin antagonist (2.6×10^{-8} M, $n=10$) caused opposite changes in the dynamics of vagal chronotropic effect. In both types of arrhythmia, K decreased in zones of pronounced and moderate chronotropic effect (Fig. 3). In addition, the duration of arrhythmia increased, while its intensity decreased. In arrhythmia below the lower boundary of synchronization, the differences between the maximum and minimal CC decreased from 210.8±12.8 to 178.3±12.6 msec ($p<0.05$), i.e., by 10.6% in comparison with the control.

Thus, our experiments showed the presence of a zone within CC where the magnitude of the vagal chronotropic effect several times surpassed that in other CC zones. It can be assumed that this zone reflects a critical change in the perception of vagal stimuli by the sinus node: even a small shift of vagal stimulus converts maximum chronotropic effect to minimum, and vice versa. It can therefore be hypothesized that changes in the amplitude of fluctuation of pacemaker sensitivity to the vagal stimuli are an important mechanism underlying peptide-induced modulation of the parasympathetic chronotropic effect under conditions of synchronized vagal and cardiac rhythms or in sinus arrhythmia.

On the other hand, the shorter zone of pronounced chronotropic effect is also responsible for the potentiating vagotropic effect of the peptides. Experiments with somatostatin showed that the same change in the length of CC can be observed at a lesser shift of the vagal stimulus within CC. A lower perception of vagal stimulus in the zone of moderate chronotropic effect can be attributed to a higher content of cholinesterase in pacemaker cells [5] and, consequently, to a more rapid hydrolysis of acetylcholine released from VN endings. Specifically, in sinus arrhythmia above the upper boundary of synchronization this zone is located before the P wave and lasts for 250-300 msec (Fig. 1), which is comparable to the latency of parasympathetic chronotropic effects [7], and therefore any shift of vagus stimulus within this zone can affect only the duration of subsequent CC. In this case the effect is weakened, since a great portion of acetylcholine is hydrolyzed at the beginning of depolarization. This is why in arrhythmia below the lower boundary of synchronization K coefficient is higher in the zone of moderate chronotropic effect: a shift of vagal stimulus is observed at the beginning of CC, therefore, it modulates the duration of the current P—P interval.

The study was supported by the Russian Foundation for Basic Research (grant 95-04-12874a).

REFERENCES

1. E. V. Montsevichyute-Eringene, *Pat. Fiziol.*, No. 4, 71-78 (1964).
2. V. M. Pokrovskii, *Fiziol. Zh.*, **74**, No. 2, 259-264 (1988).
3. V. M. Pokrovskii, O. E. Osadchii, and A. N. Kurzanov, *Byull. Eksp. Biol. Med.*, **114**, No. 7, 15-17 (1992).
4. Yu. R. Sheikh-Zade and V. M. Pokrovskii, *Ibid.*, **99**, No. 4, 393-394 (1985).
5. T. N. James and C. A. Spence, *Anat. Rec.*, **155**, 151-162 (1966).
6. M. N. Levy, P. Martin, T. Iano, and H. Zeiske, *Circ. Res.*, **25**, No. 9, 303-314 (1969).
7. M. N. Levy, P. Martin, T. Iano, and H. Zeiske, *Am. J. Physiol.*, **218**, 1256-1262 (1970).
8. V. M. Pokrovsky and O. E. Osadchiy, *Can. J. Physiol. Pharmacol.*, **73**, 1235-1245 (1995).