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PROLONGED INHIBITION OF CARDIAC VAGAL ACTION FOLLOWING SYMPATHETIC STIMULATION AND GALANIN IN ANAESTHETIZED CATS

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SUMMARY

1. Stimulation of the right cardiac sympathetic nerve for 3 min at 16 Hz in the presence of effective β-adrenoceptor blockade evoked prolonged attenuation of cardiac vagal action in the cat: $40{\cdot}8 \pm 5{\cdot}4$ % maximum inhibition of cardiac vagal action on prolonging pulse interval, with half-time to recovery of $8{\cdot}3 \pm 1{\cdot}4$ min.

2. Intravenous injection of galanin (1·6–3·1 nmol/kg) evoked prolonged attenuation of cardiac vagal action: $40{\cdot}9 \pm 8{\cdot}2$ % maximum inhibition with a half-time to recovery of $13{\cdot}6 \pm 2{\cdot}6$ min. This effect of galanin was not significantly different from the action of sympathetic nerve stimulation. A slight depressor response ($-14{\cdot}4 \pm 1{\cdot}9$ mmHg) was seen in nine of sixteen cats.

3. Intravenous injection of neuropeptide Y (NPY) (2·8–6·3 nmol/kg) evoked slight attenuation of cardiac vagal action: $11{\cdot}9 \pm 4{\cdot}5$ % maximum inhibition of cardiac vagal action on pulse interval, with a half-time to recovery of $4{\cdot}1 \pm 1{\cdot}7$ min. Blood pressure increased by $68{\cdot}6 \pm 5{\cdot}7$ mmHg.

4. Following administration of guanethidine (1 mg/kg I.V.) the inhibitory effect of sympathetic nerve stimulation on cardiac vagal action was significantly reduced ($P < 0{\cdot}001$). The responses to exogenous NPY and galanin on vagal action were unchanged after guanethidine.

5. The prolonged attenuation of cardiac vagal action can be mimicked by exogenous galanin in the cat but not by exogenous NPY.

INTRODUCTION

Galanin is a twenty-nine amino acid peptide, first isolated in 1983 from porcine intestine. Its amino acid sequence differs from other known peptides, so it is not a member of a known peptide family (Tatemoto, Rökaeus, Jörnvall, McDonald & Mutt, 1983). Its name is derived from the fact that in the porcine sequence its N- and C-terminal residues are glycine and alanine, respectively (Tatemoto *et al.* 1983).

Galanin appears to be predominantly a neuropeptide, and has been found to be widely distributed in the gastrointestinal and urogenital tracts, the central nervous system, and in various endocrine tissues of a number of species, including man (Rökaeus, 1987). Its actions in these tissues are wide-ranging, and vary according to

the particular tissue involved. Thus in the gut it can cause direct contraction of the smooth muscle (Rökaeus, Melander, Hökfelt, Lundberg, Tatemoto, Carlquist & Mutt, 1984), and in the gut, bladder and central nervous system it causes a presynaptic inhibition of evoked acetylcholine release (Yau, Dorsett & Youther, 1986; Maggi, Santiciolo, Patacchini, Turini, Barbanti, Beneforti, Guiliana & Meli, 1987; Fisone, Wu, Consols, Nordström, Brynne, Bartfai, Melander & Hökfelt, 1987; Chatterjee, Ball, Proby, Burrin & Bloom, 1988). Galanin is able to inhibit dopamine release in the central nervous system (Nordström, Melander, Hökfelt, Bartfai & Goldstein, 1987), and basal insulin release from the endocrine pancreas in the dog (Dunning & Taborsky, 1988). In the vas deferens it potentiates the contractions induced by noradrenaline, by a postsynaptic mechanism (Ohhashi & Jacobowitz, 1985).

Of particular interest to the present study was the discovery of galanin in postganglionic neurons of feline cervicothoracic sympathetic ganglia. These neurons also displayed immunoreactivity to neuropeptide Y (NPY; Kummer, 1987). Recent work (Potter, 1984, 1985) has pointed to a powerful and potentially important physiological role for NPY in the control of heart rate in anaesthetized dogs. Short periods (1–2 min) of stimulation of the sympathetic nerves to the heart inhibited the ability of the vagus nerve to slow the heart for several minutes to over an hour afterwards, through a presynaptic inhibition of acetylcholine release. This effect could be mimicked by intravenous administration of NPY (Potter, 1985, 1987). Immunoreactivity to NPY has been found in the stellate ganglion and sympathetic neurons supplying the heart (Gu, Adrian, Tatemoto, Polak, Allen & Bloom, 1983; Darvesh, Nance, Hopkins & Armour, 1987) and in the pig its release has been measured in association with cardiac sympathetic nerve stimulation (Rudehill, Sollevi, Franco-Cereceda & Lundberg, 1986). It was proposed by Potter that the prolonged vagal inhibition following cardiac sympathetic nerve stimulation was due to the NPY released from these nerves (Potter, 1985).

The presence of galanin in the cardiac sympathetic neurons of the cat suggested that it may play a role in the control of heart rate in this species. Its co-localization with immunoreactive indicators of both NPY and noradrenaline (Kummer, 1987) also indicated a possible physiological role for galanin in the cat.

The present study investigated the effects of stimulation of the cardiac sympathetic nerves on vagally mediated cardiac slowing in anaesthetized cats, to determine whether this produces a similar inhibition of cardiac vagal action to that documented in dogs, and tested both exogenous galanin and NPY to compare with the vagal inhibitory effects caused by such stimulation.

METHODS

The experiments were performed on sixteen adult cats of both sexes, weighing between 2·0 and 5·0 kg. They were anaesthetized with pentobarbitone sodium (Nembutal, Abbott Laboratories, Sydney), administered either by intraperitoneal or intravenous injection at 30–40 mg/kg. The animals were intubated, and ventilated using a small-animal respiratory pump (Harvard model 607A), adjusted to maintain end-tidal P_{CO_2} at approximately 40 mmHg. Propranolol was administered at 1·5 mg/kg in all experiments. This dose was sufficient to block the increase in heart rate evoked by 2 and 5 μg isoprenaline and 5 and 10 μg noradrenaline. Noradrenaline and

isoprenaline had a transient (2 min) inhibitory effect on cardiac vagal action but this was also completely blocked by this dose of propranolol.

Surgical preparation

The left femoral vein was cannulated for administration of further anaesthetic and drugs. The left femoral artery was also cannulated for the measurement of systemic arterial blood pressure, using a Statham P23 pressure transducer. Both vagus nerves were cut in the neck, and the right cervical vagus was gently freed from adjacent structures for stimulating towards the heart.

Access to the right stellate ganglion and sympathetic nerves supplying the heart was achieved by reflecting the right foreleg forwards. The muscles attaching the scapula to the thorax were first ligated and cut, allowing the scapula and foreleg to be lifted forwards to expose the rib-cage. After removal of sections of the first and second ribs, the stellate ganglion was located. The main cardio-accelerator nerve was identified by its ability to speed the heart when stimulated, and all other branches of the stellate ganglion were cut to prevent stimulation of afferent fibres to the central nervous system.

The electrocardiogram (ECG) was recorded through subcutaneous needle electrodes, and displayed on one channel of the pen recorder, and on a storage oscilloscope. The ECG was used to obtain beat-by-beat measurement of the time between heart beats (the pulse interval, PI) after processing with Neurolog Modules (Digitimer, UK). Results were expressed in terms of PI rather than heart rate because of the straight-line relationship between PI and the frequency of vagal stimulation (Katona, Poitras, Barnett & Terry, 1970; Parker, Celler, Potter & McCloskey, 1984). Recordings of PI, ECG and blood pressure were made on a Grass Polygraph pen recorder.

Experimental protocol

Platinum wire electrodes connected to a Grass S88 stimulator and stimulus isolation unit were used, both to stimulate the vagus, and for the periods of stimulation of the sympathetic nerves to the heart. Test stimuli were applied intermittently to the right vagus throughout the experiments, at 1 ms duration and supramaximal voltage ($\sim$ 40 V). Stimuli were delivered at frequencies from 2 to 6·5 Hz in trains lasting 5 s at 30 s intervals. These stimuli produced a reproducible bradycardia which was measured as an increase in PI (ΔPI). The exact stimulus frequency chosen in each animal was that which increased PI by between 200 and 300 ms, which was always less than the maximum attainable with higher frequencies of stimulation.

The vagal inhibitory effects of stimulation of the postganglionic cardiac sympathetic nerves (16 Hz, 3 min) were determined in six cats. Each of these cats was also given a dose of galanin (1·6–3·1 nmol/kg; 5–10 μg/kg) which was sufficient to cause a similar magnitude of vagal inhibition to the sympathetic stimulation. An intravenous dose of NPY (2·8–6·3 nmol/kg; 12–27 μg/kg) was also administered. The molar dose of NPY given was always 1·5–2 times the dose of galanin in any individual cat. Doses of NPY of this magnitude reliably cause a profound and prolonged cardiac vagal inhibition in the dog (Kilborn, Potter & McCloskey, 1985; Potter, 1985). This higher dose rate of NPY was chosen because, in preliminary experiments, NPY was found to have apparently less powerful inhibitory effects on the vagus than either galanin or sympathetic stimulation. NPY proved to be a strong pressor agent in the cat, and because it is known from other studies that it is a particularly powerful coronary vasoconstrictor (Allen, Bircham, Edwards, Tatemoto & Bloom, 1983; Maturi, Greene, Speir, Burrus, Dorsey, Markle, Maxwell, Schmidt, Goldstein & Patterson, 1989), even larger doses of NPY were not given, to avoid prejudicing the physiological state of the animal. Complete recovery of test vagal stimuli was allowed between each of these interventions.

In a further ten cats, the effects of cardiac sympathetic nerve stimulation (16 or 20 Hz, 1·5–3 min) on test vagal stimuli were compared with the effects of the same sympathetic stimulation applied following intravenous administration of guanethidine (1 mg/kg). This agent is known to prevent the release of both noradrenaline and NPY from sympathetic nerve terminals (Rudehill *et al.* 1986; Potter, 1988). In eight of these cats, the effects of intravenous galanin before and after guanethidine were compared, and in five of the cats, the effects of intravenous NPY on test vagal stimuli before and after guanethidine were compared.

Analysis of data

The actions of the interventions described above on the ability of standard vagal stimuli to prolong PI were measured. For each vagally induced ΔPI following the intervention, and until

recovery to control levels, a figure was obtained for the percentage inhibition caused using the formula:

$$\% \text{ Inhibition} = \frac{\Delta PI_c - \Delta PI_t}{\Delta PI_c} \times 100,$$

where the subscripts c and t refer to the control and treatment periods respectively. A linear regression line was fitted to the data, because in similar experiments in dogs (Gardner & Potter, 1988) the recovery of vagally induced ΔPI was found to be better fitted by a linear, rather than an exponential, function. The maximum reduction of ΔPI (maximum % inhibition) was calculated from this regression line, at 2 min after the cessation of sympathetic stimulation, or at 3 min after administration of galanin or NPY. These times coincide with the most frequently observed times of maximum effect. The use of the regression equation to calculate them makes the recorded values dependent upon the whole time series of readings, and not just the minimum recorded value of ΔPI. The time taken for recovery to 50% of the maximum % inhibition (t_{50}) was also calculated from the regression line.

Data are presented as mean ± standard error of the mean. The vagal inhibitory effects of sympathetic stimulation at 16 Hz for 3 min, I.V. galanin, and I.V. NPY were analysed, and compared by repeated-measures analysis of variance, with the significance of specific contrasts found by the least significant difference test. Paired t tests were used to compare the vagal inhibitory actions of sympathetic stimulation, galanin and NPY, before and after guanethidine treatment.

RESULTS

Stimulation of the right cardiac sympathetic nerves in the presence of effective β-adrenoceptor blockade in six cats resulted in a mean (± S.E.M.) maximum percentage inhibition of subsequent cardiac vagal action of 40·8 ± 5·4%, with a time to half-recovery of 8·3 ± 1·4 min. Stimulation of the right cardiac sympathetic nerve before administration of propranolol also resulted in attenuation of subsequent cardiac vagal action. Maximum percentage inhibition and half-time to recovery were not significantly different. Exogenous galanin (1·6–3·1 nmol/kg) in these cats caused a mean maximum percentage inhibition of 40·9 ± 8·2%, and a time to half-recovery of 13·6 ± 2·6 min. These effects of sympathetic stimulation and galanin injection were not significantly different. Exogenous NPY, in a greater molar dose than galanin, caused a mean maximum percentage inhibition of 11·9 ± 4·5%, with a time to half-recovery of 4·1 ± 1·7 min. Both of these values were less than the responses obtained following either galanin injection or sympathetic stimulation. These results are summarized in Table 1. Data recorded from a typical experiment are illustrated in Fig. 1.

When the percentage inhibition and half-time for recovery of vagal action caused by galanin and NPY were compared, galanin was found to be a significantly more powerful inhibitor of cardiac vagal action than NPY (Table 1). This was so even though galanin was administered at lower molar doses than NPY (Table 1).

In a further ten cats, the effect of guanethidine on the response to sympathetic stimulation was investigated. Before guanethidine, the vagal inhibition in response to sympathetic stimulation in these animals was 37·5 ± 4·7%, and the time to half-recovery was 11·2 ± 1·7 min. After guanethidine treatment, both of these values were significantly reduced (paired t test, $P < 0·001$) to 8·0 ± 4·1% and 1·7 ± 0·9 min for maximum percentage inhibition and time to half-recovery respectively. Guanethidine treatment had no demonstrable effect on the vagal inhibition caused by either exogenous galanin ($n = 8$) or exogenous NPY ($n = 5$) in these cats. The effects of

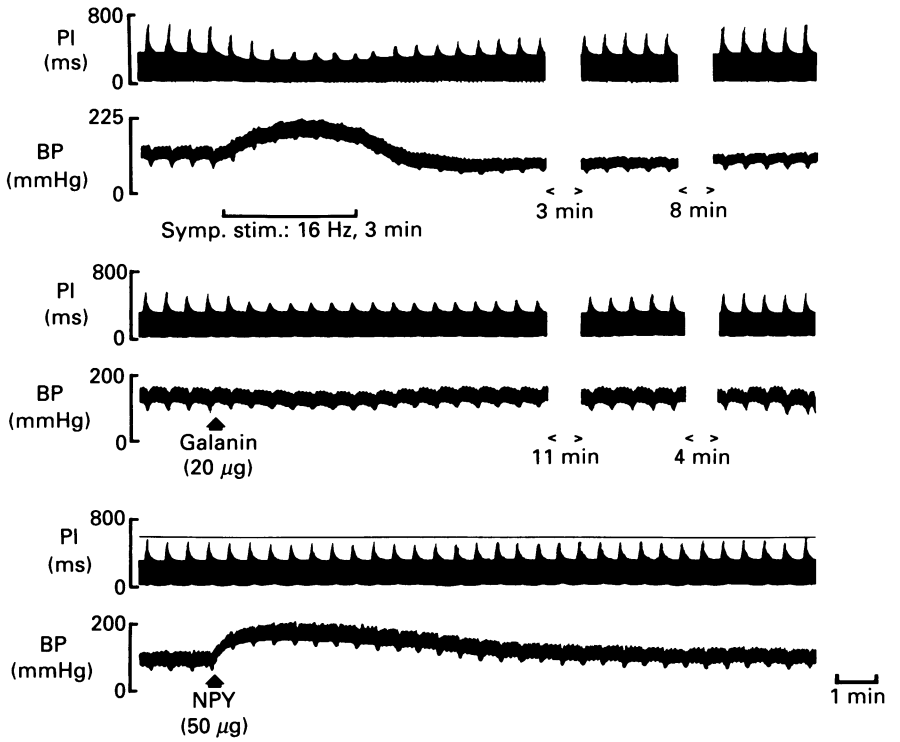

Fig. 1. Records of pulse interval (PI) and blood pressure (BP) from an anaesthetized cat, showing the effects of stimulation of the cardiac sympathetic nerve, intravenous galanin and intravenous NPY. All experiments were carried out in the presence of effective β-adrenoceptor blockade. An increase in PI was evoked every 30 s by stimulating the peripheral, cut end of the right vagus. Sympathetic stimulation caused a long-lasting inhibition of cardiac vagal action. Galanin caused a similar long-lasting attenuation of vagal effects on pulse interval. Galanin also had a slight depressor action. NPY caused only a marginal inhibition of vagally induced changes in PI. NPY was a powerful pressor agent.

TABLE 1. Effects of galanin, NPY and cardiac sympathetic stimulation on vagal action.

Experiment	Dose/stim. frequency	% Inhibition (mean ± S.E.M.)	Level of significance	Half-time recovery (mean ± S.E.M.)	Level of significance
Galanin ($n = 6$)	1·6–3·1 nmol/kg	40·9 ± 8·2	n.s.*	13·6 ± 2·6	n.s.*
NPY ($n = 6$)	2·8–6·3 nmol/kg	11·9 ± 4·5	$P < 0·01$**	4·1 ± 1·7	$P < 0·01$**
Sympathetic stimulation ($n = 6$)	16 Hz, 3 min	40·8 ± 5·4	$P < 0·01$***	8·3 ± 1·4	n.s.***

* On comparison by analysis of variance of effects of galanin and sympathetic stimulation.
** On comparison by analysis of variance of effects of NPY and galanin.
*** On comparison by analysis of variance of the effects of NPY and sympathetic stimulation.

sympathetic stimulation before and after guanethidine on vagally induced changes in PI in a typical experiment are illustrated in Fig. 2.

Overall, in the sixteen cats in the experiments, sympathetic stimulation (16 or 20 Hz, 1·5–3 min) evoked a large pressor effect of 74·7 ± 9·1 mmHg, presumably due

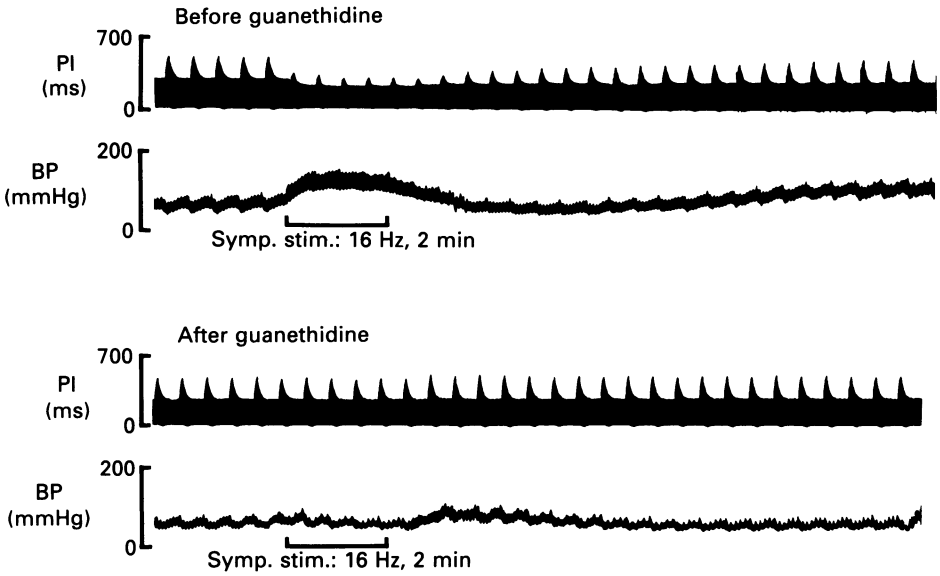

Fig. 2. Records of pulse interval (PI) and blood pressure (BP) from an anaesthetized cat, showing the effect of sympathetic stimulation on vagally induced changes in pulse interval before and after guanethidine (1 mg/kg, I.V.). Experiments were carried out in the presence of effective β-adrenoceptor blockade. An increase in PI was evoked every 30 s by stimulating the cut, peripheral end of the right vagus nerve at 2 Hz. The vagal inhibitory action of sympathetic stimulation is abolished by guanethidine, and the effects on blood pressure are markedly attenuated.

at least in part to the effects of released noradrenaline on the heart, despite the presence of the competitive β-adrenoceptor antagonist propranolol. In nine of the cats, a secondary, transient depressor response of 14·4 ± 1·9 mmHg followed this. Administration of galanin (1·6–7·8 nmol/kg; 5–25 μg/kg) had an initial small and transient pressor action in ten of fourteen cats. Overall, galanin caused a small reduction in blood pressure of 10·4 ± 1·8 mmHg, 1·5–5 min after its administration. Blood pressure returned to control levels within 8 min. NPY was found to be a powerful pressor agent in the cats, increasing the blood pressure by 68·6 ± 5·7 mmHg (n = 11). The peak pressure was achieved 1–3 min after NPY administration, with a gradual return to control levels over a period of 15–25 min.

DISCUSSION

Stimulation of the cardiac sympathetic nerves in the cat caused a long-lasting attenuation of subsequent cardiac vagal action. This vagal attenuation was similar in maximal extent to that seen following periods of stimulation of the sympathetic

nerves to the heart in the dog. However, rather longer periods of inhibition occur in dogs. For example, Hall, Gardner & Potter (1990) reported half-times to recovery of $18{\cdot}1 \pm 2{\cdot}2$ min in dogs, compared with $8{\cdot}3 \pm 1{\cdot}4$ min here. In the dog, where exogenous NPY is able to mimic the effects of sympathetic stimulation, available evidence indicates that the vagal attenuation is due to the release from the sympathetic nerves of NPY, or an NPY-like substance (see Potter, 1988, for review).

The current experiments suggest that NPY is not primarily responsible for the vagal inhibition which follows similar sympathetic stimulation in the cat. Although immunoreactivity to both NPY and galanin has been detected in feline post-ganglionic sympathetic neurons supplying the heart (Kummer, 1987), NPY had little or no vagal inhibitory action in the cats in the present study. Similar doses of NPY reliably cause prolonged vagal attenuation following intravenous administration in anaesthetized dogs (Kilborn *et al.* 1985; Potter, 1985). In contrast, the vagal attenuation following galanin administration was significantly greater than that following intravenous NPY, despite the higher molar doses of NPY used in the comparison. On this basis, galanin seems a more likely candidate than NPY as a mediator of the prolonged vagal inhibitory effects of sympathetic stimulation in the cat.

It is known that guanethidine blocks both noradrenaline and NPY release from sympathetic nerve terminals (Lundberg, Änggård, Theodorsson-Norheim & Pernow, 1984; Rudehill *et al.* 1986). In similar experiments in dogs, guanethidine blocked the vagal inhibition seen following sympathetic stimulation, but not that due to exogenous NPY (Potter, 1987*b*). In the present study guanethidine reduced or abolished the vagal inhibition due to cardiac sympathetic nerve stimulation, but not that due to exogenous galanin, or, where it had an effect, exogenous NPY. It is therefore likely that guanethidine also blocked release of the vagal inhibitory substance (possibly galanin) from sympathetic nerve terminals here.

We are not able to say how galanin or NPY acts in the cat from our experiments. However, in dogs and in isolated guinea-pig atria, it has been shown that NPY inhibits release of acetylcholine from the vagus, thus reducing vagal effectiveness at the heart (Potter, 1987*a*). It has been demonstrated that galanin is able to suppress acetylcholine release in other tissues such as the gut, bladder and in the central nervous system (Yau *et al.* 1986; Maggi *et al.* 1987; Fisone *et al.* 1987; Chatterjee *et al.* 1988) so, possibly, a similar mechanism operates for its cardiac vagal inhibitory actions.

The effects in cats of NPY and galanin on systemic blood pressure were of interest. NPY was found to be a powerful pressor agent, as has been shown in other species (Lundberg & Tatemoto, 1982; Potter, 1985; Mabe, Perez, Tatemoto & Huidoboro-Toro, 1987). Galanin, on the other hand, at lower molar doses, had primarily a modest depressor effect, although in about 70% of the animals studied a small, transient pressor effect was also seen very soon after administration of galanin.

Thus, a comparison of the effects of sympathetic stimulation, NPY and galanin on vagal actions at the heart suggests that, in the cat, the effects of sympathetic stimulation may be mediated mainly by the release of galanin, and possibly also of NPY, from these nerves.

It is interesting to speculate on the possible physiological significance of this

phenomenon which we are suggesting is based on NPY in the dog and galanin in the cat. Through it, the cardiac vagus is weakened in its ability to slow the heart for a long period after sympathetic stimulation. This may ensure that cardiac output does not return immediately to control levels after the sympathetic activation that accompanies muscular exercise, an action that may be important in the restoration of the metabolic status of the previously active muscle.

Other possible functions may suggest themselves when the whole range of physiological actions of NPY and galanin are documented, such actions might include metabolic and trophic effects of the peptides.

We believe, also, that there is possible pathophysiological significance in this phenomenon through which the heart 'remembers' a period of sympathetic activation for a long time after it has ceased. Possible relations between stress and hypertension might be based on such phenomena.

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