Journal of Physiology (1993), **469**, *pp.* 37–50
With 5 figures
Printed in Great Britain

DIFFERENTIAL SYMPATHETIC REACTIONS DURING CEREBRAL ISCHAEMIA IN CATS: THE ROLE OF DESYNCHRONIZED NERVE DISCHARGE

BY BERNAT KOCSIS, LASZLO FEDINA, KATALIN GYIMESI-PELCZER, TEREZ LADOCSI AND EMIL PASZTOR

From the Department of Physiology, National Institute of Neurosurgery, Budapest, H-1145, Amerikai ut 57, Hungary

(*Received 24 February 1992*)

SUMMARY

1. Sympathetic nerve discharge (SND) of three postganglionic nerves with different functions and anatomical locations was simultaneously recorded at rest and during severe cerebral ischaemia (Cushing reaction). The three nerves, controlling the heart (inferior cardiac nerve), visceral (renal nerve) and skeletal muscle circulation (vertebral nerve), were selected with the assumption that their activity pattern will represent the differential central autonomic command to the major players of the circulatory response to cerebral ischaemia.

2. Changes in the power density spectra of the nerve signals, and in the pairwise coherence functions, elicited by the cerebral ischaemia, were evaluated separately for the rhythmic (R-SND, i.e. between 0 and 6 Hz) and high-frequency (HF-SND, i.e. between 12 and 100 Hz) components of the nerve signals.

3. The sympathetic nerve response to cerebral ischaemia developed in two phases. Phase 1 was a massive R-SND reaction and phase 2 was characterized by SND desynchronization and by the emergence of HF-SND. The power of HF-SND occupied a wide band between 12 and 80 Hz with maximum between 20 and 30 Hz. All three nerves were involved in the Cushing response but the magnitude and character of the reactions were specific for each nerve. In the cardiac nerve, the power of the rhythmic component of the discharge increased almost twice the control and remained dominant during the whole reaction, strongly modulating HF-SND during the second phase. In the vasomotor nerves, R-SND was suppressed during phase 2 and HF-SND occupied 65% of the total power of the signal. Near equal R- to HF-SND proportions, however, were reached on different activity levels in renal and vertebral nerves. Whereas total renal SND did not change, the power of the vertebral SND increased more than twice. In addition, desynchronization in the vertebral SND was preceded by a massive R-SND reaction during phase 1, which was missing in the renal nerve.

4. For all possible nerve pairs, R-SND was highly coherent before the reaction and remained so during intracranial pressure elevation, regardless of the direction and magnitude of the changes in absolute and/or relative power of this component in different nerves. On the other hand, HF-SND never correlated between any of the

nerve pairs indicating that this component in each nerve originated from specific sources of regional sympathetic activity.

5. We conclude that the sympathetic nervous system is capable of generating different types of activity, including rhythmic and desynchronized discharges, and these activity patterns play an important role in generating differential sympathetic nerve response to cerebral ischaemia. Different sympathetic networks controlling different cardiovascular effectors, due to their specific properties (i.e. unequal capability of synchronization or desynchronization of the discharge), may convert the general excitatory effect of the cerebral ischaemia into specific discharge patterns with characteristic involvement of rhythmic and non-rhythmic components.

INTRODUCTION

The sympathetic nervous system is capable of generating differentiated patterns of peripheral nerve activity in different experimental conditions (Ninomiya, Nisimaru & Irisawa, 1971; Kollai, Fedina & Kovach, 1973; Kollai, Koizumi & Brooks, 1978; Weaver, Fry & Meckler, 1984; Janig, 1985; Weaver, Meckler, Tobey & Stein, 1986; Dean & Coote, 1986). It can also develop global functional states in which a large part of the system (or the whole) may produce uniform reactions (Cannon, 1929). These two aspects are often treated as contrasting one another, although attempts for their reconciliation within a concept of hierarchical organization were also made (Khayutin, Sonina & Lukoshkova, 1977). An important mechanism of co-operation between sympathetic neurons projecting through the same postganglionic nerves is the synchronization of their discharge in a periodic fashion producing slow waves in the multi-unit nerve recording (Adrian, Bronk & Phillips, 1932; Bronk, Ferguson, Margaria & Solandt, 1936; Cohen & Gootman, 1970; Gootman & Cohen, 1973; Gebber, 1980). The physiological significance of changes in the frequency characteristics of such synchronization (e.g. switch of the cardiac related rhythmic activity to regular 10 Hz oscillations in certain behavioural states) was underscored by recent studies in awake cats (Matsukawa & Ninomiya, 1987; Ninomiya, Nishimura, Matsukawa & Akiyama, 1989; Ninomiya, Akiyama & Nishimura, 1990). Furthermore, a high correlation between different nerves at rest was shown using different techniques both in the time and frequency domains (Gootman & Cohen, 1973; Gebber & Barman, 1980; Kocsis, Gebber, Barman & Kenney, 1990). When setting the goal of the present study, we reasoned that an investigation into the dynamics of these correlations (i.e. changes in the level of synchronization *within a nerve* bundle and of the coherence *between different nerves*) at rest and when the system is perturbed by a strong stimulus, might give some insight into the 'dualistic' (i.e. specific and integrative) nature of the autonomic regulation.

Cerebral ischaemia is one of the most powerful stimuli that can activate the sympathetic nervous system (Guyton, 1948; Brown, 1956). It evokes a circulatory reaction which is aimed at restoring the blood flow to the brain and involves both vascular and cardiac effector mechanisms. Blood flow measurements in different organs indicate that the contribution of each vascular bed to the increase in total peripheral resistance is not uniform (Dampney, Kumada & Reis, 1979; Van Wylen & D'Alecy, 1985). Sympathetic nerve recordings showed increase in the activity in

different nerves (Tanaka, Hashi, Nishimura & Matsuura, 1976; Yamamoto, Higashi, Fujii, Hayashi & Ito, 1983; Matsuura, Sakamoto, Hayashida & Kuno, 1984; Pasztor, Fedina, Kocsis and Berta, 1986; Prabhakar, Mitra, Van de Graaf, Haxhiu & Cherniack, 1986). It was also found that during cerebral ischaemia not only the total activity increased but also the frequency characteristics of the SND changed (Matsuura *et al.* 1984; Kocsis, Fedina & Pasztor, 1989). During the first part of the reaction the sympathetic nerve discharge (SND) increased in amplitude and frequency but remained rhythmic. After some time the SND desynchronized and high-frequency components started to dominate the nerve signals. These changes were reversible and could be repeated many times in the same animal (Kocsis, Fedina & Pasztor, 1991*a*).

In the present study we recorded from three different nerves representing the nervous outflows to the heart (inferior cardiac nerve) and to the visceral (renal nerve) and skeletal muscle vasculature (vertebral nerve) at rest and during severe cerebral ischaemia and compared their reactions by means of spectral analysis of the SNDs. The changes in power were calculated separately for the rhythmic (R-SND) and the high-frequency desynchronized (HF-SND) components of the neurograms and the linear relationship between the signals was tested using the coherence function. At rest, the power spectra of these SNDs are very similar and there is a high coherence between each pair of these three nerves (Kocsis *et al.* 1990). However, the coherence can considerably decrease during asphyxia and the power spectra can change in different ways both during asphyxia and cerebral ischaemia (Kocsis, Gebber & Fedina, 1991*b*). The purpose of the present quantitative analysis was to determine if the changes in different frequency bands have any regional specificity and whether these SND components are generated by specific or related neural circuits.

METHODS

We used adult cats weighing between 3·2 and 4·1 kg that were anaesthetized by the intraperitoneal injection of a mixture of α-chloralose (50 mg/kg) and urethane (200 mg/kg), and paralysed with pipecuronium bromide (every 45 min at a dose of 0·05 mg/kg). Body temperature was maintained between 38 and 39 °C with a heating pad. A femoral artery was cannulated and a tracheostomy tube was inserted, low in the neck. The cats were artificially respired. The CO_2 concentration in the expired air was monitored (Datex Normocap) and the end-tidal CO_2 was maintained near 4%. A femoral vein was cannulated to permit intravenous administration of drugs and anaesthetic. Administration of the muscle relaxant and artificial ventilation started after all surgery was completed and when it was necessary to use bilateral pneumothorax to ensure stable nerve recording. The adequacy of anaesthesia was evaluated using the electroencephalogram, the electrocardiogram (heart rate) and the systemic arterial pressure. Supplementary doses of anaesthetic (10–20% of the initial dose) were given intravenously as needed. The level of the anaesthesia used in this study had also proved to be adequate in earlier experiments in which no muscle relaxants were used. The arterial baroreceptors were left intact in all experiments.

Surgery

Three sympathetic postganglionic nerves were prepared on the left side for simultaneous electrophysiological recording. The vertebral and inferior cardiac nerves were approached dorsolaterally. After removing the head of the first rib the stellate ganglion was exposed retropleurally. The vertebral nerve exits this ganglion in the cranial direction and follows the route of the vertebral artery into the cervical channel where it branches and joins the massive nerve trunks of the cervical plexus at several levels. For good recording, this nerve has to be carefully desheathed because in most cases there is a somatic nerve running within the same connective

tissue sheath which may shunt the current generated by the sympathetic fibres. The inferior cardiac nerve was located within the same pool, exiting the ganglion in a caudo-ventral direction. The left renal nerve was dissected retroperitoneally through another dorsolateral incision. All nerves were cut peripherally and their central ends were placed on fine platinum electrodes and covered by warm liquid paraffin.

The Cushing reaction was evoked 1–4 times in each experiment using the standard technique described in detail in our previous publications (Kocsis *et al.* 1989, 1991*a*; see these references also for a review of the strong correspondence between changes in brain metabolism and sympathetic nerve activity during cerebral ischaemia elicited by intracranial pressure elevation and arterial occlusion). Briefly, a hollow needle was inserted into the cisterna magna and safely fixed to the head-holder. Care was taken not to damage the medulla while puncturing the atlanto-occipital membrane. The free end of the needle was connected through a T-tube to the infuser and a pressure transducer. Intracranial pressure was increased to 130–200 mmHg by infusion of 1–5 ml of artificial cerebrospinal fluid. The infusion was not stopped until desynchronization of SND (i.e. phase 2, see Kocsis *et al.* 1989) was achieved in at least one of the nerves.

Data recording and analysis

The data for this study were collected before and during eighteen epochs of intracranial hypertension in eleven cats. The signals recorded from the three nerves were amplified with differential amplifiers with bandpass setting of 1·5 Hz–1·5 kHz. The neurograms together with arterial pressure, intracranial pressure, and expired CO_2 concentration were recorded on a polygraph (Minograph 82, Siemens-Elema) that was able to record high-frequency signals up to 1·2 kHz. SNDs and SAP were also stored on magnetic tape (Ampex) for further off-line computer analysis. These signals were then filtered (low-pass, 300 Hz) and sampled at 1 kHz with a fast analog-to-digital converter (RC Electronics).

Power density spectra (autospectra) and coherence functions were computed on fifteen to forty windows of 1 s duration and averaged, as described earlier (Kocsis *et al.* 1990). This paper can also be referred to for details on the computational algorithm, significance testing, and interpretation of the information provided by such analysis. In short, the autospectrum of a signal shows the distribution of power (voltage squared) at different frequencies. The area under the power density spectrum between two particular frequencies represents the mean square value of the record associated with that frequency range. The total area under the autospectrum over all frequencies (i.e. 'total power') will be the total mean square value of the record (Bendat & Piersol, 1986). The coherence function shows how linear correlation of the two signals varies as a function of frequency. The average autospectra as represented in the figures of this paper are displayed on a scale of 0–50 Hz to show both R- and HF-SND. The amplitude of the autospectra in the figures is autoscaled to the highest peak and the coherence functions are represented on a scale of 0–1. The power of each signal was computed separately in different frequency bands, e.g. between 0 and 6 Hz for characterization of R-SND and between 12 and 100 Hz to characterize HF-SND. A relatively wide intermediate zone was set between 6 and 12 Hz for safe separation of these two major components of SND from each other and also from the possible 10 Hz component of R-SND (Cohen & Gootman, 1970; Ninomiya *et al.* 1990). Changes in all parameters during phase 1 and phase 2 of the Cushing reaction are expressed as a percentage of the control values computed from spontaneous SND immediately before the start of the intracranial pressure elevation. Differences of group means over control and different phases of the reaction were tested by the analysis of variance and pooled pairwise *t* tests.

The relationship between different nerve pairs and between each nerve and the blood pressure (BP) was evaluated separately for R- and HF-SND by computing the peak and the mean coherences within the corresponding frequency bands. Statistical comparison of the correlations between different nerve pairs was avoided because ordinary coherence in this experimental design (i.e. highly correlated discharge in all possible nerve pairs of the same nerve triple) is unable to separate the 'true' pairwise correlation from that imposed by the influence of the third SND or sources common for all three nerves, e.g. baroreceptor input (Bendat & Piersol, 1986; Kocsis, 1992).

RESULTS

As described earlier, the sympathetic nerve response to severe cerebral ischaemia develops in two phases. During phase 1 there is a massive increase in the rhythmic SND and phase 2 is characterized by SND desynchronization and the emergence of HF-SND. Although these changes sometimes occur simultaneously in the different nerves (Fig. 1*A*), in most reactions, both the rhythmic and the high-frequency

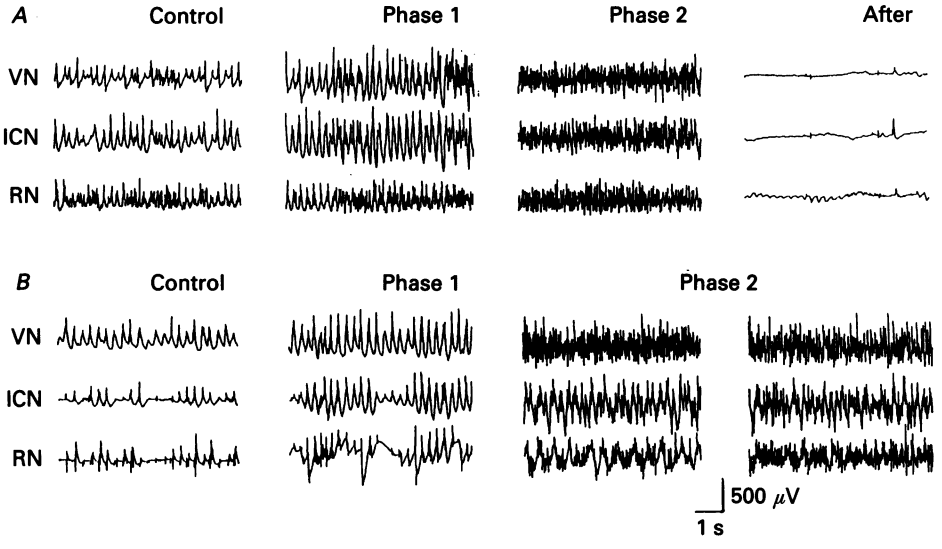

Fig. 1. Typical changes in sympathetic nerve discharge during severe cerebral ischaemia, in two cats (*A* and *B*): rhythmically synchronized discharge pattern in all nerves during a control period (control); increase in amplitude and frequency of slow waves during phase 1 of cerebral ischaemia (phase 1); desynchronization of discharge during phase 2 of cerebral ischaemia (phase 2). Activity was recorded simultaneously in three nerves: vertebral nerve (VN), inferior cardiac nerve (ICN), and renal nerve (RN), on the left side. In cat *A* complete desynchronization occurred simultaneously in all nerves. In cat *B* there was a differential response in which complete desynchronization occurred in the vasomotor nerves (RN lagged behind VN) while high-frequency discharge appeared rhythmically modulated in the cardiac nerve. Complete cessation of activity in all nerves (background noise level) after the intracranial pressure dropped to normal level (After).

components of the discharge exhibit marked regional differences. In the representative example shown in Fig. 1*B*, phase 1 was very similar in all three nerves. Phase 2 started with desynchronization of the vertebral SND that was not, however, immediately accompanied by analogous changes in the other two nerves. HF-SND did appear in the cardiac and renal nerves as well, but it was periodically synchronized by a less regular R-SND component (Fig. 1*B*, phase 2, on left). Later, R-SND diminished also in the renal nerve and only occupied a considerable part of the cardiac nerve activity (Fig. 1*B*, phase 2, on the right).

Power spectra

Power spectra of the control records showed the characteristics of the typical resting R-SND of the anaesthetized baroreceptor-intact cat (Fig. 2). Most of the power, in each SND, was below 6 Hz within a relatively narrow band around the only

peak at 2–3 Hz. In some cases, renal SND was slightly different from the other two nerves in that the tail of its unimodal spectrum extended into the higher frequency range. Figure 2 demonstrates the changes in the SND power density spectra during four episodes of cerebral ischaemia, in one cat. In the vertebral nerve, R-SND

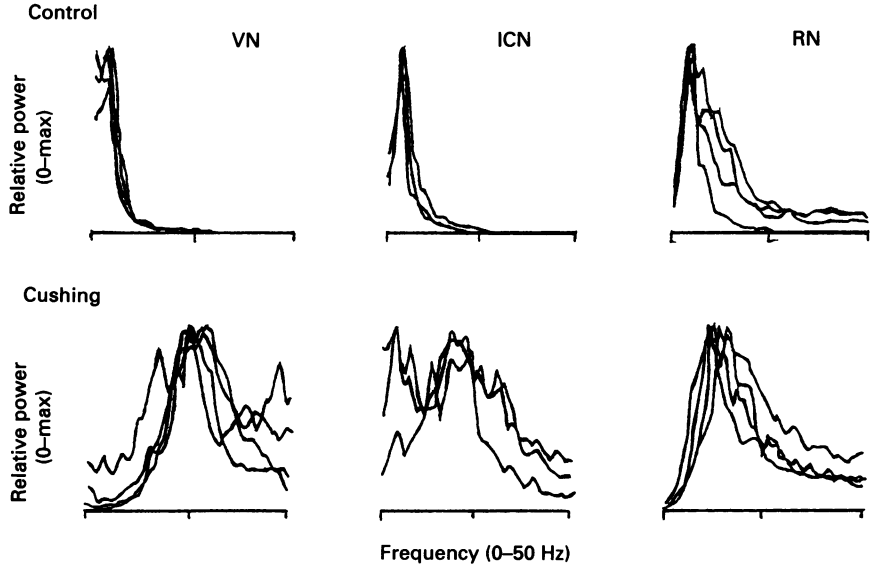

Fig. 2. Power density spectra of discharges in vertebral (VN), inferior cardiac (ICN), and renal (RN) nerves in a control period (control) and during phase 2 of severe cerebral ischaemia (Cushing) elicited by rapid intracranial pressure elevation. Autospectra of VN and RN corresponding to four, and of ICN corresponding to three reactions in the same cat are superimposed (there was no ICN recording during one of the reactions). The autospectra were calculated on the basis of 21–28 windows of 1 s duration with 50% overlap, and were normalized so that relative power is plotted against frequency. Control period was chosen immediately before the start of intracranial infusion and had an equal length with the corresponding phase 2 segment.

disappeared in all reactions and it was completely replaced by a desynchronized discharge. The spectrum of the vertebral HF-SND occupied a wide band between 12 and 80 Hz with a less stable maximum between 20 and 30 Hz. Similar HF-SND was also apparent in the cardiac nerve. The rhythmic component in this nerve did not, however, vanish and its peak, in two out of three reactions, was comparable with the amplitude of the HF-SND maximum. The renal autospectrum also shifted to higher frequencies and was considerably dispersed.

Quantitative analysis of eighteen reactions in eleven cats (Fig. 3 and Table 1) revealed that all three nerves were involved in the sympathetic reaction to cerebral ischaemia, but the magnitude and character of the changes were specific for each SND. On the group average, total SND power increased in the vertebral (VN) and cardiac (ICN) nerves but not in the renal nerve (RN). Complete desynchronization occurred in the vasomotor nerves (i.e. VN and RN) while rhythmic modulation of the discharge persisted in the cardiac nerve.

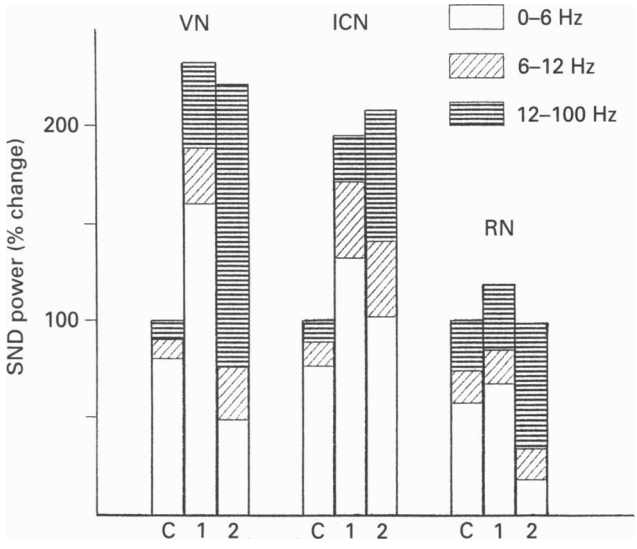

Fig. 3. Responses in vertebral (VN), inferior cardiac (ICN) and renal (RN) nerves to severe cerebral ischaemia. Bars represent averages of power, expressed as a percentage of control, in different frequency bands corresponding to R-SND (0–6 Hz), HF-SND (12–100 Hz) and an intermediate zone (6–12 Hz) between them, for control (C), phase 1 (1) and phase 2 (2) of Cushing reaction in 11 cats. Significant changes occurred in total power of VN and ICN. Changes in distribution of power between different frequency bands (i.e. desynchronization) were significant in all nerves but significantly higher in the vasomotor nerves (VN or RN) than in ICN.

TABLE 1. Changes in the distribution of power (area under the autospectrum within a certain frequency band) between rhythmic and non-rhythmic components of the sympathetic nerve discharge during cerebral ischaemia

	Total			R-SND			HF-SND		
	Ctr	Ph1	Ph2	Ctr	Ph1	Ph2	Ctr	Ph1	Ph2
Distribution of power (%)									
VN				80	69	22	10	19	66
ICN		100		76	68	49	11	12	32
RN				57	56	19	26	29	65
Change in power (%)									
VN	100	233	222	100	201	61	100	443	1465
ICN	100	195	208	100	174	134	100	213	605
RN	100	119	98	100	117	33	100	133	245

R-SND and HF-SND, rhythmic and high-frequency sympathetic nerve discharge; Ctr, control; Ph1, phase 1; Ph2, phase 2. VN, vertebral nerve; ICN, inferior cardiac nerve; RN, renal nerve. Distribution of power, percentage of total power within the characteristic frequency ranges (i.e. R-SND: 0–6 Hz and HF-SND: 12–100 Hz); Change in power, percentage change in power from control (Ctr) to phase (Ph1) and phase 2 (Ph2) of cerebral ischaemia.

R-SND

During phase 1, the power between 0 and 6 Hz doubled in the vertebral and cardiac but did not change in the renal nerve. During phase 2, the regional differences were even more remarkable. The R-SND directed to the heart remained hyperactivated (134% of control) resulting in strong rhythmic modulation of the emerging cardiac HF-SND. At the same time, the absolute power of R-SND dropped in the two vascular nerves (61 and 33% of control). It is worth noting that the relative proportions of R-SND in these nerves were nearly equal (22 and 19%), even though the total integrated activity was still doubled in the vertebral and was close to the control level in the renal nerve.

HF-SND

During the second phase, the absolute increase in power at frequencies above 12 Hz was much higher in the vertebral SND than in the other two nerves. HF-SND in this nerve increased as much as 14 times (range, 4·24–20·33) relative to the control and comprised 66% of the signal during phase 2 of the reaction. There was also a tremendous enhancement of high-frequency components in the cardiac and renal nerve activities (605 and 245%, ranges 293–974 and 210–704, respectively) which, however, was not as great as the rise in the vertebral HF-SND.

Although all experiments were made in baroreceptor-intact animals, in four cats, during the control period, there was no coherence between the SNDs and arterial pressure (see details below). This may be very important both for the total SND response as well as its frequency characteristics. Therefore, these four experiments were separated and the averages of the spectral characteristics were recalculated for this group alone. The only significant difference between this group and the whole sample was related to the changes in the R-SND in the inferior cardiac nerve. In this group the enhanced cardiac R-SND could not be maintained over the second phase (as a percentage of control, R-SND in this nerve increased to 165% during phase 1 and 100% during phase 2).

Variations of the Cushing reaction between animals related mainly to the proportions of the R- and HF-SND in different nerves (Fig. 4). The reaction in the vertebral SND was the most stable of all nerves. Complete desynchronization in this nerve was present in all trials without exception. In the cardiac nerve, strong R-SND persisted during both phases of the reaction. A low-frequency peak was present within the 0–6 Hz range in sixteen cases and between 6 and 12 Hz in the remaining two experiments. This peak either had an amplitude comparable with that of the HF-SND maximum, e.g. in Fig. 4*A* and *B*, or one that considerably exceeded it, as in Fig. 4*C* and *D*. This latter pattern in a few experiments appeared also in the renal autospectra (Fig. 4*D*). In most cases, however, renal SND had two peaks of similar amplitude, one below 6 Hz and another one above 12 Hz.

Coherences

In the resting state, pairwise coherences are different from zero over the whole R-SND frequency range, suggesting that individual rhythmic nerve activities are, in part, derived from common or related sources. Changes in these coherences during the Cushing response would have indicated a disproportionate activation of the

common and specific rhythm generators contributing to the regional sympathetic outflow. However, this did not happen. Mean coherence between different nerve pairs was between 0·38 and 0·56 before the cerebral ischaemia and remained in the same range during the first phase (i.e. the phase of R-SND activation). During the second

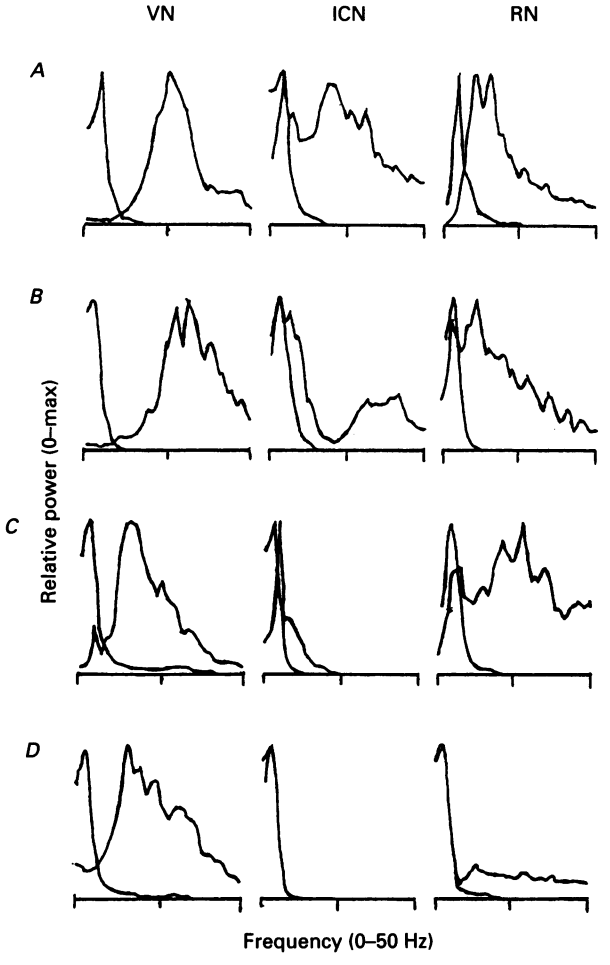

Fig. 4. Varieties of Cushing reactions in four different cats with different proportions of power at low (i.e. between 0 and 6 Hz) and high (i.e. above 12 Hz) frequencies, in three nerves (vertebral, VN; inferior cardiac, ICN; renal, RN). In each plot, autospectra for a control period and the period of phase 2 of cerebral ischaemia were autoscaled separately and superimposed. Note that because of the autoscale, these plots can only depict the *relative* amplitude of different peaks. For instance, in *D*, power of the high-frequency component increased 201 % relative to the control in ICN and comprised 24 % of the total power of the signal. This cannot be seen in the figure since the resolution of the plot has been determined by the 5·37-fold increase in power concentrated within a narrow band below 6 Hz whereas HF-SND dispersed over a wide range of frequencies.

phase, the coherences decreased but remained significantly different from zero (Table 2). In individual experiments, whenever the rhythmic components were present in two nerves during the cerebral ischaemia, the nerve activities also remained correlated (e.g. ICN–RN in Fig. 5). On the other hand, the coherence between 0 and

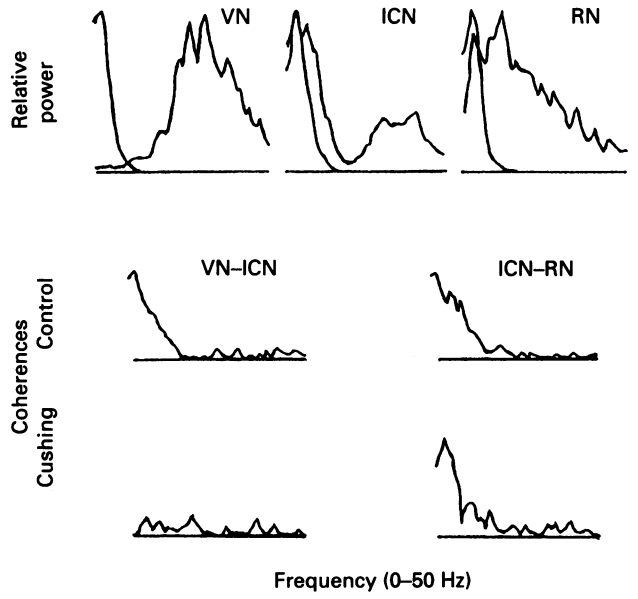

Fig. 5. Autospectra of sympathetic nerve discharges in three nerves and coherences between different nerves in control and during phase 2 of cerebral ischaemia. Autospectra are presented as in Fig. 4. Coherences were scaled between 0 and 1. In control, the rhythmic components (i.e. below 12 Hz) of the SNDs were highly coherent. During cerebral ischaemia, R-SND remained correlated only for cardiac and renal nerves (ICN–RN) where both SNDs contained a relatively high peak in the low frequency range. There was no coherence above 12 Hz in any experiment, even if the power was high in this frequency band.

TABLE 2. Change in linear correlation (squared coherence) between different pairs of sympathetic nerves and between SND and arterial blood pressure during cerebral ischaemia

	Peak*			R-SND			HF-SND		
	Ctr	Ph1	Ph2	Ctr	Ph1	Ph2	Ctr	Ph1	Ph2
Nerve–nerve coherences									
VN–ICN	0·68	0·67	0·60	0·56	0·55	0·46	0·04	0·05	0·05
VN–RN	0·53	0·51	0·44	0·38	0·38	0·29	0·02	0·03	0·05
ICN–RN	0·64	0·58	0·53	0·47	0·43	0·38	0·02	0·03	0·05
BP–nerve coherence									
BP–VN	0·33	0·38	0·28	0·23	0·24	0·16			
BP–ICN	0·30	0·37	0·26	0·25	0·23	0·14		n.s.	
BP–RN	0·33	0·32	0·24	0·21	0·21	0·14			

BP, arterial blood pressure.

* Peak coherence was calculated as the maximal coherence at the dominant frequency for nerve pairs and at the heart rate for blood pressure and nerve activity.

6 Hz became very low if there was no significant power left in this band, other than the low-frequency tail of the HF-SND (see VN autospectrum and coherences between VN and ICN in Fig. 5).

Desynchronized SND was different in this respect. Unlike the rhythmic discharge, HF-SND never correlated in any of the nerve pairs indicating that this component in each nerve originated from individual sources of regional sympathetic activity.

In the control records, significant coherences were found between the arterial pressure and the SND in seven cats. During the Cushing reaction, the group averages of both the peak and the 0–6 Hz mean coherences remained significantly different from zero (Table 2). The relationship between the arterial pressure and the SNDs, however, was not stable. There were various changes in the individual experiments, in both directions. Even in phase 2, where the BP-to-SND coherences decreased in most reactions, significant increase was evident in some experiments. Evidently, there was no coherence between the blood pressure and the SND at higher frequencies.

DISCUSSION

The results presented here are in agreement with numerous earlier reports of the powerful pressor response, increase of total peripheral resistance and cardio-acceleration mediated by the sympathetic nervous system during cerebral ischaemia (Guyton, 1948; Brown, 1956; Ganaka *et al.* 1976; Matsuura *et al.* 1984; Pasztor *et al.* 1986; Kocsis *et al.* 1989). Earlier blood flow measurements in different organs during the Cushing reaction (Dampney *et al.* 1979; Van Wylen & D'Alecy, 1985) suggested a generalized increase in the sympathetic activity with quantitative differences between different nerves. The present experiments provide new information on the mechanism of this nervous reaction. We found that differential sympathetic control involves not only uneven augmentation of the regional nervous outflow but also non-uniform changes of the *discharge pattern*, in different sympathetic efferents. After a transient increase, the R-SND, dominated by 1–6 Hz rhythmic slow waves, switched to a more powerful high-frequency discharge. Complete desynchronization was characteristic for the vasomotor SNDs. In these nerves, during the second phase of the reaction, HF-SND was also the main carrier of the regional differences. On the other hand, rhythmic synchronization of the cardiac nerve activity remained strong and could not be suppressed by HF-SND, during the whole reaction.

Although it has not been emphasized, similar SND desynchronization appeared in other sympathetic reactions reported earlier. For example, Gootman & Cohen (1970) reported spontaneous increase in the splanchnic nerve activity associated with arterial hypertension. Their Fig. 1 shows desynchronization of the SND, too. Similarly, Fig. 4 of the report by Weaver *et al.* (1984) shows desynchronized discharge in the splenic nerve after atrial bradykinin injection. Electrical stimulation of the hypothalamic defense area (see Fig. 3 in Dean & Coote, 1986) and of the pressor area in the medulla (see Fig. 1 in Gootman & Cohen, 1973) also appears to be able to desynchronize renal and splanchnic SNDs. All these experiments used strong sympathoexcitatory stimuli and were aimed at modelling extreme physiological and pathological conditions. Similarly, during cerebral ischaemia, SND desynchronization occurs only if the ischaemia is severe (Kocsis *et al.* 1989). For intracranial hypertension this means a decrease of the cerebral perfusion pressure below the autoregulatory range (Kocsis & Lenkei, 1992).

The high functional capacity of the HF-SND corresponds to the emergency character of the reactions in which it appears. Renal vasoconstriction, for instance, is so severe during cerebral ischaemia that it may lead to anaemia of the kidney (Murata & Miyakawa, 1967; Dampney *et al.* 1979). Since total power of the renal SND did not change and its R-SND component decreased considerably, this could only be associated with the switch of the nerve activity to a desynchronized discharge pattern. It is to be expected that SND desynchronization plays an analogous role in other vascular beds since the level of arterial hypertension is significantly higher during the second than the first phase of the Cushing reaction (Kocsis *et al.* 1989).

Furthermore, great regional differences in the reactivity of this SND component suggest that HF-SND is a potential mediator of *differential* sympathetic reactions. Although the degree of desynchronization (i.e. R- to HF-SND ratio) was nearly equal in the two vasomotor nerves, the increase in power of the fast activity in the vertebral nerve exceeded that in the renal nerve several times.

The functional significance of the disproportional activation of the muscular and visceral SNDs may be related to the non-uniformities in the innervation of these two divisions of the circulation. Changes in the vascular resistance during massive sympathoactivation is dependent upon the combined α- and β-effects of the catecholamines released not only at the sympathetic nerve terminals but also from the adrenal medulla.

α-Adrenergic receptor blockade (Van Wylen & D'Alecy, 1985) or sympathetic denervation (Dampney *et al.* 1979) reversed the cerebral ischaemic response to vasodilatation in the femoral bed whereas some residual vasoconstriction persisted in the kidney. β-Adrenergic receptor blockade or bilateral adrenalectomy, on the other hand, unmasked a strong vasoconstriction also in the skeletal muscle mediated by the sympathetic nerves. Thus the regional SND, while acting in concert with humoral catecholamines to increase the vascular resistance in the kidney, tries to counterbalance the strong β-mediated vasodilatation in the femoral bed.

Frequency characteristics of the cardiac SND were clearly different from those of the vasomotor nerves. Although HF-SND was present in this nerve as well, the cardiac sympathetic generator was able to keep the high level of R-SND during both phases of the reaction. R-SND also increased in the vertebral nerve at the beginning of the cerebral ischaemia but it vanished during the second phase, as the power of HF-SND increased. The functional significance of the greater capacity of the cardiac nerve to generate synchronized discharge in the 1–6 Hz range remains to be determined. It may be related to the rhythmic nature of the effector controlled by this nerve. It might also play a certain role in making the structures generating cardiac nerve activity more susceptible to phasic baroreceptor influences.

Coherence spectral analysis showed that SND desynchronization means disruption of the co-ordinated discharge not only within a nerve bundle but between different nerves, as well. The coherence between HF-SND in any nerve pair was always zero. Therefore, this component of the regional sympathetic activity originates from unrelated sources that makes it a suitable object for selective control by the higher sympathetic centres.

On the other hand, differential changes in power of the SND within the 0–6 Hz

range were not accompanied by corresponding changes in the nerve-to-nerve coherences. During phase 1, the coherence *did not increase* between the vertebral and cardiac nerves, even though these two R-SNDs changed in the same direction, and *did not decrease* between the renal SND and any of the other nerves, despite the quite disproportional changes in the power of the corresponding R-SNDs. This means that the proportion of the common and specific sources of the R-SNDs remained unaltered during the complex two-phase differential reaction.

In conclusion, there are important differences between the organization of the central circuits generating sympathetic nervous outflows to different cardiovascular effectors which include non-uniform potential to synchronize or desynchronize the discharge during extreme sympathoexcitatory reactions. Due to their specific properties, these circuits were capable of converting the general excitatory effect of cerebral ischaemia into specific discharge patterns in three postganglionic efferents subserving different physiological functions.

REFERENCES

ADRIAN, E. D., BRONK, D. W. & PHILLIPS, G. (1932). Discharges in mammalian sympathetic nerves. *Journal of Physiology* **74**, 115–133.

BENDAT, J. S. & PIERSOL, A. G. (1986). *Random Data. Analysis and Measurement Procedures.* John Wiley & Sons, New York.

BRONK, D. W., FERGUSON, L. K., MARGARIA, R. & SOLANDT, D. Y. (1936). The activity of the cardiac sympathetic centers. *American Journal of Physiology* **117**, 237–249.

BROWN, F. K. (1956). Cardiovascular effects of acutely raised intracranial pressure. *American Journal of Physiology* **185**, 510–514.

CANNON, W. (1929). *The Wisdom of the Body.* Norton, New York.

COHEN, M. I. & GOOTMAN, P. M. (1970). Periodicities in efferent discharge of splanchnic nerve of the cat. *American Journal of Physiology* **218**, 1092–1101.

DAMPNEY, R. A. L., KUMADA, M. & REIS, D. J. (1979). Central neural mechanisms of the cerebral ischemic response. Characterization, effect of brainstem and cranial nerve transactions, and simulation by electrical stimulation of restricted regions of medulla oblongata in rabbit. *Circulation Research* **45**, 48–62.

DEAN, C. & COOTE, J. H. (1986). Discharge patterns in postganglionic neurones to skeletal muscle and kidney during activation of the hypothalamic and midbrain defence areas in the cat. *Brain Research* **377**, 271–278.

GEBBER, G. L. (1980). Central oscillators responsible for sympathetic nerve discharge. *American Journal of Physiology* **239**, H143–155.

GEBBER, G. L. & BARMAN, S. M. (1980). Basis for 2–6 cycle/s rhythm in sympathetic nerve discharge. *American Journal of Physiology* **239**, R48–56.

GOOTMAN, P. M. & COHEN, M. I. (1970). Efferent splanchnic activity and systemic arterial pressure. *American Journal of Physiology* **219**, 897–903.

GOOTMAN, P. M. & COHEN, M. I. (1973). Periodic modulation (cardiac and respiratory) of spontaneous and evoked sympathetic discharge. *Acta Physiological Polonica* **24**, 97–109.

GUYTON, A. C. (1948). Acute hypertension in dogs with cerebral ischemia. *American Journal of Physiology* **154**, 45–54.

JANIG, W. (1985). Organization of the lumbar sympathetic outflow to skeletal muscle and skin of the cat hindlimb and tail. *Reviews in Physiology, Biochemistry and Pharmacology* **102**, 119–213.

KHAYUTIN, V. M., SONINA, R. S. & LUKOSHKOVA, E. V. (1977). *Central Organization of Vasomotor Control.* Medicina, Moscow.

KOCSIS, B. (1992). Whether there are differential relationships among discharges of postganglionic sympathetic nerves remains an open question. *American Journal of Physiology* **261**, R717–719.

KOCSIS, B., FEDINA, L. & PASZTOR, E. (1989). Two-phase change of sympathetic rhythms in brain ischemia, Cushing reaction, and asphyxia. *American Journal of Physiology* **256**, R120–132.

KOCSIS, B., FEDINA, L. & PASZTOR, E. (1991*a*). Effect of preexisting brain ischemia on sympathetic nerve response to intracranial hypertension. *Journal of Applied Physiology* **70**, 2181–2187.

KOCSIS, B., GEBBER, G. L., BARMAN, S. M. & KENNEY, M. J. (1990). Relationships between activity of sympathetic nerve pairs: phase and coherence. *American Journal of Physiology* **259**, R549–560.

KOCSIS, B., GEBBER, G. L. & FEDINA, L. (1991*b*). Common and specific sources of regional sympathetic outflows in cerebral ischemia, Cushing reaction, and asphyxia. In *Cardiorespiratory and Motor Coordination*, ed. KOEPCHEN, H. P. & HUOPANIEMI, T., pp. 16–25. Springer, Berlin.

KOCSIS, B. & LENKEI, Z. (1992). Coordination of cardiovascular and respiratory control systems during and after cerebral ischemia. *Journal of Applied Physiology* **72**, 1595–1603.

KOLLAI, M., FEDINA, L. & KOVACH, A. G. B. (1973). Effect of bleeding, cooling and asphyxia on the activity of vertebral and cardiac sympathetic nerves. *Acta Physiologica Academiae Scientiarum Hungaricae* **44**, 145–155.

KOLLAI, M., KOIZUMI, K. & BROOKS, C. McC. (1978). Nature of differential sympathetic discharges in chemoreceptor reflexes. *Proceedings of the National Academy of Sciences of the USA* **75**, 5239–5243.

MATSUKAWA, K. & NINOMIYA, I. (1987). Changes in renal sympathetic nerve activity, heart rate and arterial blood pressure associated with eating in cats. *Journal of Physiology* **390**, 229–242.

MATSUURA, S., SAKAMOTO, H., HAYASHIDA, Y. & KUNO, M. (1984). Efferent discharges of sympathetic and parasympathetic nerve fibers during increased intracranial pressure in anesthetized cats in absence and presence of pressor response. *Brain Research* **305**, 291–301.

MURATA, A. & MIYAKAWA, K. (1967). Periodic changes in resistance of renal vascular bed during systemic blood pressure oscillation in rabbits. *Medical Journal of Shinshu University* **12**, 273–297.

NINOMIYA, I., AKIYAMA, T. & NISHIURA, N. (1990). Mechanism of cardiac-related synchronized cardiac sympathetic nerve activity in awake cats. *American Journal of Physiology* **259**, R499–506.

NINOMIYA, I., NISIMARU, N. & IRISAWA, H. (1971). Sympathetic nerve activity to the spleen, kidney, and heart in response to baroreceptor input. *American Journal of Physiology* **221**, 1346–1351.

NINOMIYA, I., NISHIURA, N., MATSUKAWA, K. & AKIYAMA, T. (1989). Fundamental rhythm of cardiac sympathetic nerve activity in awake cats at rest and during body movement. *Japanese Journal of Physiology* **39**, 743–753.

PASZTOR, E., FEDINA, L., KOCSIS, B. & BERTA, Z. (1986). Activity of peripheral sympathetic efferent nerves in experimental subarachnoideal hemorrhage. Part I. Observations at the time of intracranial hypertension. *Acta Neurochirurgica* **79**, 125–131.

PRABHAKAR, N. R., MITRA, J., VAN DE GRAAF, W., HAXHIU, M. A. & CHERNIACK, N. S. (1986). Effect of focal cooling of central chemosensitive areas on cerebral ischemic response. *American Journal of Physiology* **251**, R295–302.

TANAKA, K., HASHI, K., NISHIMURA, S. & MATSUURA, S. (1976). Changes of sympathetic vasomotor activity during increased intracranial pressure. In *Intracranial Pressure III*, ed. BEKS, J. W. F., BOSCH, D. A. & BROCK, M., pp. 50–57. Springer, Berlin.

VAN WYLEN, D. G. L. & D'ALECY, L. G. (1985). Regional blood flow distribution during the Cushing response: alterations with adrenergic blockade. *American Journal of Physiology* **248**, H98–108.

WEAVER, L. C., FRY, H. K. & MECKLER, R. L. (1984). Differential renal and splenic nerve responses to vagal and spinal afferent inputs. *American Journal of Physiology* **246**, R78–87.

WEAVER, L. C., MECKLER, R. L., TOBEY, J. C. & STEIN, R. D. (1986). Organization of differential sympathetic responses to activation of visceral receptors and arterial baroreceptors. In *Central and Peripheral Mechanisms of Cardiovascular Regulation*, ed. MAGRO, A., OSSWALD, W., REIS, D. & VANHOUTTE, P., pp. 269–301. Plenum, New York.

YAMAMOTO, S., HIGASHI, S., FUJII, H., HAYASHI, M. & ITO, H. (1983). Vasomotor response in acute intracranial hypertension. In *Intracranial Hypertension V*, ed. ISHII, S., NAGAI, H. & BROCK, M., pp. 335–337. Springer, Berlin.