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The Influence of Bilateral Electrical Preganglionic Sympathetic Stimulation on Intra- and Extracranial Blood Flow

Lars-Owe D. Koskinen

Department of Physiology and Medical Biophysics, Biomedical Centre, University of Uppsala, Uppsala, Sweden

ABSTRACT

The effects of bilateral electrical stimulation (SS) of the cervical sympathetic chain on intra- and extra cerebral blood flows were studied with the labelled microsphere method in the rabbit. Control blood flow was determined before the SS was started. The stimulation frequency was 7 Hz, the impulse duration 2 ms, the intensity 7V and the stimulation time varied between 1 to 5 minutes before the second blood flow determination.

Arterial blood gas values and blood pressure were unaffected by the stimulation. Due to the SS there were blood flow decrements in the extracranial tissues between 60-96%. The blood flow in the eyes, the dura, pineal gland and choroid plexa was markedly reduced during the SS. No obvious effect was elicited by the SS in the regional or total cerebral blood flow. The stimulation to control blood flow ratio ranged between 0.92 $\pm$ 0.08 to 1.13 $\pm$ 0.09 in different parts of the brain.

The conclusions are that SS elicits vasoconstriction in several extra- and intracranial nonneuronal tissues and in the eye. Cerebral blood flow is not influenced by the SS.

INTRODUCTION

The cerebral vasculature is innervated by several types of nerves, particularly by sympathetic nerve fibres emanating from the superior cervical ganglion. The influence of these sympathetic nerves on cerebral blood flow has been evaluated in several species and under a variety of conditions and with conflicting results (9, 17, 19). In the conscious and anaesthetized rabbit at its normal blood pressure no obvious tonic influence of the cervical sympathetic nerves was detected on regional (rCBF) and total (CBF_{tot}) cerebral blood flow, but on extracranial blood flows (10-13). The electrical stimulation of the sympathetic chain unilaterally did not markedly influence the cerebral blood flow in the normotensive cat (3), monkey (1) and rabbit (5, 15). In acute hypertension, on the other hand, sympathetic stimulation has a clear protective effect, preventing cerebral hyperemia and disruption of the blood-brain-barrier (4, 8). Indeed, in the normotensive

animal an "escape phenomenon" from the sympathetic influence on the cerebral vessels has been proposed. Thus, in the rabbit a decrease in CBF was shown early in the course of stimulation of the cervical sympathetic chain (18) while Beausang-Linder & Hultcrantz (5) found no such effect.

It has been speculated that, due to a double (ipsi and contralateral cervical sympathetic) innervation of the cerebral vessels a more pronounced effect could be elicited by bilateral stimulation. Indeed, it was recently reported by Busija (6, 7) that the bilateral, but not unilateral, stimulation of the cervical sympathetic ganglion at 8 and 16 Hz considerably reduced the cerebral blood flow in the rabbit.

The present investigation was undertaken in order to elucidate whether 1) bilateral preganglionic cervical sympathetic stimulation at a frequency regarded as being the upper part of the physiological range influences rCBF and CBF_{tot} and 2) whether nonneural intracranial tissues are affected by the stimulation and 3) to what extent ocular and extracranial tissues are affected.

METHODS

Seven New Zealand albino rabbits of either sex weighing between 1.7-4.0 kg were used. The animal was anesthetized with a 25 % solution of urethane i.v. in a dose of 7 ml kg^{-1} b.w. The animal was tracheotomized and ventilated by a Palmer pump. Mean arterial blood pressure (MAP) measurements, with a Druck PDCR 75/1 transducer and an Servogor 460 recorder, and blood sampling was conducted from a pair of cannulated arteries. The regional blood flow was measured by the labelled microsphere method (2, 20). Microspheres were injected directly into the left ventricle through a cannula introduced retrogradely via the left brachial artery. Spheres, 15 um in diameter (NEN, Boston, Massachusetts, USA), labelled with ^{95} Nb, ^{103} Ru and ^{141} Ce were used . One femoral vein was cannulated and used for drug injections.

The cervical sympathetic chain was bilaterally identified and sectioned about one centimeter below the upper cervical ganglion. The distal part of the sympathetic nerve was bilaterally isolated, covered with mineral oil, and electrically stimulated with bipolar silver electrodes. Care was taken not to stimulate the aortic depressor nerve. The stimulator (Digitimer DS9A, Welwyn Garden City, England) was operated at a stimulatory frequency of 7 Hz, intensity 7 V and impulse duration 2 ms.

The first microsphere injection was performed under resting conditions. The nerve was then bilaterally stimulated for 3 to 5 min (in one case 1 min) before, during and 1 min after the second microsphere injection.

Arterial blood gases (P_aO_2 and P_aCO_2) and pH were measured at intervals with an ABL2 acid-base analyzer (Radiometer, Copenhagen, Denmark). If needed, sodium bicarbonate was given i.v. to correct deviations in pH. Pancuronium bromide (Pavulon^R, Organon, Oss, Holland) was administered in a dose of 0.05-0.2 mg/kg in order to induce

skeletal muscle relaxation. The body temperature was recorded by a rectal thermistor and maintained at about 38-39°C with a heating pad. Heparin, 500 IU/kg b.w. was used as anticoagulant.

After the experiment the animal was sacrificed by an i.v. injection of saturated KCl. Organs and tissue samples from organs were excised and placed in preweighed plastic tubes. Gray matter from the frontal and occipital cortex, hippocampal region, caudate nucleus, thalamic region, hypothalamic region, collicule, pons-mesencephalon, medulla oblongata, cerebellum and spinal cord were excised. Total CBF was calculated as including all regions except the medulla oblongata, cerebellum and spinal cord. The eye was dissected into the retina, choroid, iris and ciliary processes. Various other tissues were also sampled. The radioactivity of blood and tissue samples was determined by gamma spectrometry. Blood flows were calculated according to the free flow method (2).

All results are presented as means ± SEM. Statistical evaluations of the means was performed with the two-tailed Student' s t-test for paired observations.

RESULTS

In the control situation the cardiovascular variables were within the normal range, and did not change during nerve stimulation (Table 1). Mydriasis was observed on both sides during the stimulation. There was no difference in blood flow between the two sides, and the duration of stimulation did not influence the response. Therefore pooled data were used in the calculations of means.

Table 1

Arterial blood gases, pH and MAP before and during bilateral cervical sympathetic stimulation. Pressures are expressed in kPa. Mean ± SEM.

	MAP	P_aO_2	P_aCO_2	pH_a
Control	11.0 ± 0.7	13.7 ± 0.7	4.2 ± 0.2	7.44 ± 0.02
Stimulation	11.0 ± 0.9	13.8 ± 0.8	4.3 ± 0.1	7.42 ± 0.02

As shown in Figure 1, bilateral sympathetic stimulation caused blood flow decrements between 60 and 96 % in some extracranial tissues. The most reactive tissues were the masseter muscle ($p<0.001$) and tongue ($p<0.001$), while the weakest response was detected in the parietal bone ($p<0.001$) and thyroid gland ($p<0.001$). The control blood flow was in these tissues 134 ± 38, 66 ± 19, 6 ± 1 and 33 ± 6 g min^{-1} per 100g, respectively. An intermediate effect of the nerve stimulation was observed in the parotid gland

($p<0.001$) with a baseline blood flow of 63 ± 18 g min^{-1} per 100g and in the upper incisive ($p<0.001$), the control blood flow being 15 ± 2 g min^{-1} per 100g.

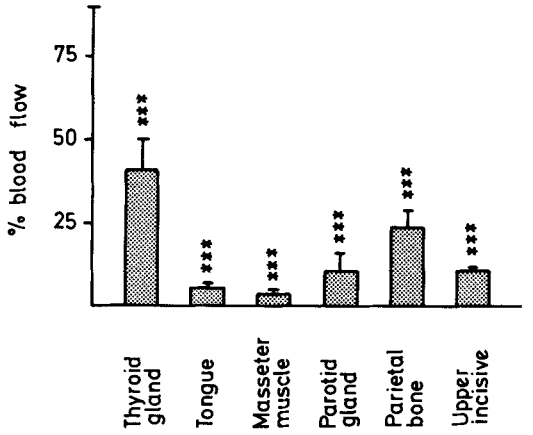

Fig.1. Percentage extracranial blood flows during bilateral sympathetic stimulation as compared with unstimulated condition. *** $p<0.001$. Mean ± SEM.

Figure 2 depicts the stimulation effect on ocular blood flow and some intracranial blood flows. The normal blood flow in the retina was 10 ± 2, choroid 1067 ± 220, iris 82 ± 12 and ciliary processes 123 ± 30 mg min^{-1}. The sympathetic stimulation caused a marked reduction in all parts of the eye ($p<0.001$). Dural and pineal gland control blood flow was 51 ± 7 g min^{-1} per 100g and 24 ± 4 mg min^{-1}, respectively and decreased significantly ($p<0.001$) during nerve stimulation. A 20% decrease ($p<0.02$) was detected in the choroid plexus which had a baseline blood flow of 34 ± 4 mg min^{-1}.

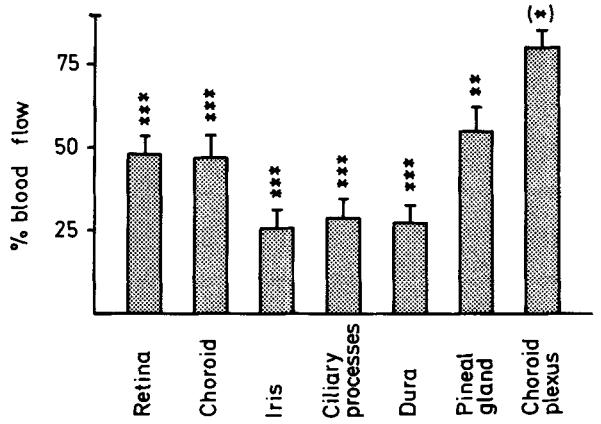

Fig.2. Percentage ocular and some intracranial blood flows during bilateral sympathetic stimulation as compared with unstimulated condition. (*) $p<0.02$, ** $p<0.01$ and *** $p<0.001$. Mean ± SEM.

There was no obvious effect of the sympathetic stimulation on the total or regional cerebral blood flow (Table 2). As expected, the highest rCBF was found in the caudate nucleus and cortical gray matter. CBF_{tot} was 57 ± 6 during control condition and 58 ± 6 g min^{-1} per 100g during the bilateral sympathetic stimulation. The highest stimulation to control ratio, 1.13 ± 0.09, was found in the caudate nucleus and the lowest, 0.92 ± 0.08, in the hypothalamic region and, 0.92 ± 0.10, in the cerebellum.

Table 2

Regional cerebral and spinal cord blood flow before and during bilateral stimulation of the cervical sympathetic chain. The stimulation to control blood flow ratio is also shown. Values in g min^{-1} per 100g. Mean ± SEM.

	Control	Stimulation	Stimulation/Control
CBF_{tot}	57 ± 6	58 ± 6	1.03 ± 0.07
Gray matter	71 ± 11	74 ± 10	1.10 ± 0.10
White matter	51 ± 4	47 ± 3	0.94 ± 0.06
Hippocampal region	35 ± 2	35 ± 4	0.98 ± 0.07
Caudate nucleus	80 ± 6	90 ± 9	1.13 ± 0.09
Thalamic region	66 ± 9	64 ± 9	0.99 ± 0.06
Hypothalamic region	40 ± 6	36 ± 5	0.92 ± 0.08
Collicles	60 ± 7	59 ± 6	0.99 ± 0.07
Pons-Mesencephalon	43 ± 4	45 ± 4	1.06 ± 0.10
Medulla oblongata	41 ± 6	40 ± 5	1.01 ± 0.11
Cerebellum	61 ± 12	52 ± 7	0.92 ± 0.10
Spinal cord (C_1-C_3)	21 ± 3	22 ± 3	1.12 ± 0.12

DISCUSSION

The present investigation shows that extra- and nonneural intracranial tissues are markedly affected by bilateral sympathetic stimulation. Thus, all tissues investigated showed a decreased blood flow during the sympathetic stimulation. The decrements exceeded 50 % in all tissues excluding the pineal gland and choroid plexus from the lateral ventricle. The vasoconstriction in the choroid plexus was of the same magnitude as that elicited by unilateral cervical sympathetic stimulation (5). In the present study the effect persisted throughout the stimulatory period which was not the case in the former investigation. Therefore the bilateral stimulation does not seem to be more

efficient in eliciting vasoconstriction but probably exerts a more durable effect. The control blood flows of the dura and eye were similar to those reported by Linder (15), and the magnitude of vasoconstriction was similar to that during unilateral sympathetic stimulation. Taken together these results suggest that bilateral sympathetic stimulation has little or no additional effect on tissue blood flow as compared with the effects elicited by unilateral stimulation of the cervical sympathetic chain.

Concerning the CBF, it has been shown that, using stimulus parameters similar to those in the present study, bilateral stimulation of the superior cervical ganglion of the rabbit elicited about 20 % decrease in CBF (7). This effect was stable throughout the stimulatory period which ranged from 1 to 6 minutes (6, 7). In the present study no obvious effect on rCBF and CBF_{tot} was observed. However, there were some differences in the experimental procedure. In our study preganglionic cervical sympathetic stimulation at 7 Hz was used whereas Busija stimulated at a frequency of 8 Hz directly on the ganglion. Furthermore, our rabbits were anaesthetized with urethane, and pentobarbital-chloralose was used in the other investigation. It is well known that the reduction in CBF produced by barbiturate anaesthesia is greater than that resulting from urethane anaesthesia as compared with the conscious state (11, 16). Thus, the CBF presented by Busija is much lower than that in the present investigation. The barbiturate anaesthesia may induce a disproportionate ratio between cerebral blood flow and metabolism which may be influenced by sympathetic stimulation. Indeed, a transient effect of sympathetic stimulation on CBF has been shown in the rabbit, and this was affected by pentobarbital anaesthesia (18). On the other hand no influence of the unilateral sympathetic stimulation on the CBF, including the escape phenomenon, was detected by Beausang-Linder and Hultcrantz (5). It has subsequently been reported that unilateral sympathetic stimulation caused a decrease in the CBF in rabbits pretreated with yohimbine (14). Thus, an $alpha_2$-mediated mechanism could be involved in the effects exerted by the sympathetic nerves on cerebral vessel resistance and prolong the transient effect previously described. In a single experiment, the stimulation duration before microsphere injection was only one minute. No tendency to a decreased CBF was found, indicating that an escape phenomenon was not of great importance.

In conclusion, profound vascular constriction is elicited in a variety of extra- and intracranial nonneural tissues and in the eye during bilateral sympathetic stimulation. An effect on the cerebral blood flow was not detected, indicating that under resting conditions when our experimental procedure is followed, the bilateral sympathetic stimulation does not markedly influence the cerebral blood flow during the period investigated.

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Address for reprints:

Dr. Lars-Owe D. Koskinen
Department of Physiology and Medical Biophysics
Biomedical Centre
University of Uppsala
Box 572
S-751 23 Uppsala, Sweden