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Effects of raised intracranial pressure on regional cerebral blood flow: a comparison of effects of naloxone and TRH on the microcirculation in partial cerebral ischaemia

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1 The effects on regional cerebral blood flow (rCBF) of raised intracranial pressure (ICP) and of naloxone and thryrotropin releasing hormome (TRH) during this condition were studied in anaesthetized rabbits.

2 The ICP was elevated until a central ischaemic response was observed. The regional blood flow was determined with the microsphere technique before and during elevation of the ICP (ICP_e) and after drug treatment.

3 Total CBF was reduced by about 70% during ICP_e while the uveal blood flow increased slightly and some other peripheral tissue blood flows remained unaffected.

4 The administration of TRH caused an increase in mean arterial blood pressure (MAP) from 11.9 ± 0.6 to 14.6 ± 0.7 kPa and a normalization of the rCBF. In some peripheral tissues, e.g. gastric mucosa and spleen, TRH reduced the blood flow by 53% and 76%, respectively. In blood pressure stabilized animals no effect on rCBF was seen after TRH.

5 Naloxone had no consistent effect on MAP or local blood flow.

6 It was concluded that in the range of cerebral perfusion pressure studied there was a passive relationship between cerebral blood flow and perfusion pressure. The lack of effect of naloxone and the marked effect of TRH during cerebral ischaemia are consistent with a mechanism of action of TRH not related to a 'physiological' antagonism of opioids.

Introduction

Opioid peptides have been assumed to be involved in a variety of stress states such as hypovolemic, endotoxic, insulin-induced, and spinal contusion shock. Changes in 'β-endorphin like' immunoreactivity have been reported in some brain regions and blood plasma in such situations. The origin of the released β-endorphin is problematic and has been postulated to be of hypophysial origin (Holaday *et al.*, 1981a). However, opioid peptides may also be released from the adrenal gland and from other focal sites (Hosobuchi *et al.*, 1982; Holaday *et al.*, 1983). It is assumed that released endorphins in some way contribute to the blood pressure decrease seen in these conditions. The hypotension is reversed by administration of naloxone intravenously (i.v.) or intracerebroventricularly (i.c.v.); for reviews see Lang *et al.* (1982) and Holaday (1983).

In parallel with naloxone, thyrotropin releasing hormone (TRH) has been shown to have beneficial effects in many shock conditions proposed to be due to a 'physiological' opioid antagonism (Holaday *et al.*, 1981b). However, TRH can reverse experimental anaphylactic shock produced by leukotriene D_4 whereas naloxone is ineffective (Lux *et al.*, 1983). In addition, TRH has a pressor effect *per se*. Thus there seems to be a difference between the pressor effect of TRH and naloxone in both normotensive and stressed animals.

Beneficial effects of naloxone in cerebral ischaemia and of naloxone and TRH on neurological deficits have been reported (Baskin & Hosobuchi, 1981; Baskin *et al.*, 1982; Faden *et al.*, 1982a; Hosobuchi *et al.*, 1982; Naftchi & Gennaro, 1982; Faden *et al.*, 1982b; Chalif *et al.*, 1983). However, there are other reports that naloxone and TRH failed to reverse ischaemia-induced neurological deficits (Holaday &

D'Amato, 1982; Kastin *et al.*, 1982).

Various effects of opiate antagonists on cerebral blood flow (CBF) have been reported. In anaesthetized cats naltrexone produced a decrease in regional cerebral blood flow (rCBF) (Grandison *et al.*, 1982) whereas in anaesthetized dogs (Artru *et al.*, 1980) and unanaesthetized rabbits (Koskinen & Bill, 1983) an effect of naloxone was not observed. Nor was there any effect of naloxone in the *in vitro* preparation of human pial arteries (Brandt *et al.*, 1983) whereas an inhibition of vasoconstrictor effects of noradrenaline and at a higher concentration a nonspecific vasodilatation of the canine basilar arterial strip was reported by Sasaki *et al.* (1984). In anaesthetized rabbits, TRH caused an increase in rCBF (Koskinen & Bill, 1984) while no effect was observed in the *in vitro* preparation of cat cerebral arteries (Hanko *et al.*, 1982). In cerebral ischaemic baboons no effect of naloxone on CBF was observed while a decrease was detected in the cat (Baskin *et al.*, 1982; Levy *et al.*, 1982). In these animals the neurological signs were reversed by naloxone. TRH had no effect on CBF in dogs with experimental stroke and failed to reverse neurological signs in this model (Faden *et al.*, 1982a). In experimental spinal contusion, improvement in blood flow in injured tissues after administration of naloxone and TRH has been reported (Young *et al.*, 1981; Faden *et al.*, 1982b; 1983).

Because of the conflicting data on the effects of naloxone on cerebral circulation and the recently reported effect of TRH on regional cerebral blood flow in the anaesthetized rabbit, it seemed of interest to study further the effects of naloxone and TRH on local cerebral, ocular and peripheral blood flows and MAP in partial cerebral ischaemia (PCI). The purpose of the present study was also to examine whether PCI activates endorphin mechanisms with a modulating effect on the sympathetic response.

Methods

New Zealand white rabbits of either sex weighing between 2.2–2.7 kg were used. The animal was anaesthetized with a 25% solution of urethane i.v. in a dose of 7 ml kg^{-1} b.wt. The rabbit was tracheotomized and ventilated by a Palmer pump. Both femoral arteries were cannulated with polyethylene catheters, one for arterial blood pressure measurements with a Druck PDCR 75/1 transducer and a Servogor 460 recorder. The other artery was used for blood sampling. The regional blood flow was measured by the labelled microsphere method (Wagner *et al.*, 1969; Alm & Bill, 1972). Microspheres were injected directly into the left ventricle through a cannula introduced retrogradely via the left brachial artery. Spheres of 15 μm diameter, labelled with ^{95}Nb, ^{103}Ru, ^{141}Ce and ^{113}Sn were used (NEN). One femoral vein was cannulated and used for drug injections. In animals used for experiments with stabilized blood pressure a wide polyethylene catheter was inserted into the abdominal aorta about 4–5 cm below the renal arteries. This catheter was connected to an external reservoir and two smaller polyethylene catheters were inserted into the abdominal catheter. The small catheters were used for blood pressure measurement and blood sampling. In these animals i.v. injections were given via the marginal ear vein.

Arterial P_{O_2}, P_{CO_2} and pH were determined with an ABL2 acid-base analyzer (Radiometer, Copenhagen). If needed, sodium bicarbonate was given i.v. to correct deviations in pH. Pancuronium bromide (Pavulon) was given in a dose of 0.05–0.2 mg kg^{-1} 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. Unilateral cervical sympathotomy was performed in order to evaluate sympathetic effects on blood flow to the head region.

The animal was placed in a stereotaxic David Kopf instrument (Tujunga, California) and the head was fixed with lambda 1 mm below bregma. Stainless steel cannulae were inserted into both lateral ventricles of the brain using the coordinates: 7.5 mm posterior to bregma, 7.0 mm lateral to the sagittal suture and 7.0–7.5 mm deep from the outer surface of the skull. One cannula was used for ICP measurements and the second for infusion of artificial cerebrospinal fluid (CSF). For the composition of the CSF, see Sadoshima *et al.* (1981). The positions of the cannulae were identified post mortem by injecting a small amount of Evan's blue through the cannulae and during the experiments by measurement of the ICP. Heparin, 500 iu kg^{-1} b.wt. was used as anticoagulant and thereafter the animal was allowed to rest for at least 30 min.

A control blood flow measurement was then performed. The ICP was then raised by elevation of an external reservoir filled with CSF prewarmed to 38°C immediately before entering the brain. The ICP was elevated until an increase in MAP of about 1.5 kPa was achieved; this was considered a central ischaemic response. Blood pressure was allowed to stabilize for 15 min followed by the second microsphere injection. Naloxone ($n = 8$) or TRH ($n = 7$) both at 2 mg kg^{-1} b.wt. was injected i.v. and about 5 min later the third blood flow measurement was performed. In addition, some animals were treated as above but the blood pressure was stabilized at its normal level after TRH administration by removing blood into the external reservoir ($n = 4$).

The animal was killed after the third blood flow measurement by i.v. injection of saturated KCl. Organs and tissue samples from organs were dissected out and placed in preweighed plastic tubes. Grey

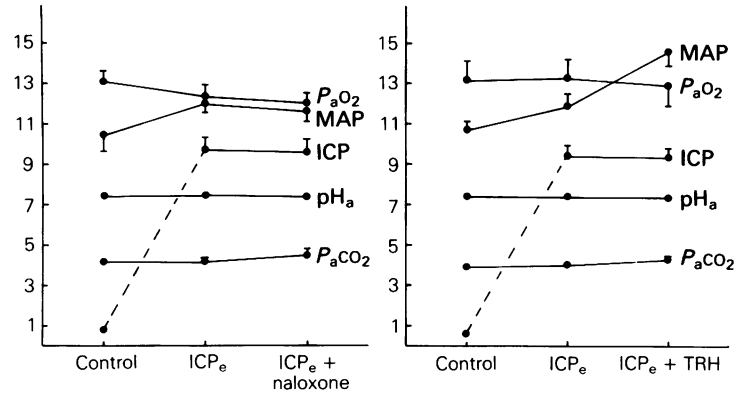

Figure 1 Arterial acid-base values, mean arterial blood pressure (MAP) and intracranial pressure (ICP) during the control situation, during elevation of the ICP (ICP_e) and during ICP_e + naloxone ($n = 8$) or TRH ($n = 7$) treatment. Pressures given in kPa.

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 dissected out. Total CBF was calculated as including all regions except the medulla oblongata, cerebellum and spinal cord. The eye was dissected into the 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 (Alm & Bill, 1972).

Pure naloxone was kindly donated by Endo Laboratories and TRH (Batch No. GA 3558) from Ferring, Malmö, Sweden.

Statistical evaluations were performed with the two-tailed Student's t test for paired observations or with analysis of variance (ANOVA) followed by the Student-Neumann-Kuels test (SNK) when needed. Two levels of significance, $P < 0.05$ and $P < 0.01$ were considered in the SNK test. Results are expressed as means ± standard error (s.e.).

Results

Figure 1 summarizes the arterial blood gas values, MAP and ICP in the control situation, after elevation of the ICP (ICP_e) and after drug treatment. Blood gas values were not greatly altered either by ICP_e or drug treatment. The cerebral perfusion pressure (CPP), defined as MAP−ICP, was markedly decreased after

Table 1 Regional cerebral and spinal cord blood flows in control situation, after elevation of intracranial pressure (ICP_e) and after ICP_e + naloxone

	Control		*ICP_e*		*Naloxone*	
	I	S	I	S	I	S
Grey matter	60 ± 13	64 ± 12	18 ± 3	16 ± 3	13 ± 2	12 ± 3
White matter	43 ± 5	41 ± 6	14 ± 5	11 ± 3	8 ± 2	8 ± 2
Hippocampal region	31 ± 2	35 ± 3	10 ± 1	11 ± 2	10 ± 2	9 ± 2
Caudate nucleus	50 ± 5	56 ± 10	21 ± 2	23 ± 7	17 ± 3	20 ± 2
Thalamic region	67 ± 10	85 ± 17	21 ± 4	29 ± 11	17 ± 4	21 ± 5
Hypothalamic region	44 ± 2	52 ± 6	15 ± 3	20 ± 4	12 ± 2	12 ± 3
Collicles	69 ± 6	70 ± 5	25 ± 4	24 ± 4	21 ± 3	18 ± 3
Pons-mesencephalon	50 ± 3	51 ± 4	22 ± 2	23 ± 4	20 ± 3	18 ± 2
Medulla oblongata	60 ± 5	58 ± 5	23 ± 2	22 ± 2	23 ± 2	22 ± 2
Cerebellum	89 ± 15	85 ± 17	25 ± 3	26 ± 3	26 ± 3	26 ± 2
Spinal cord (C_1–C_3)	38 ± 4	36 ± 4	15 ± 2	13 ± 1	14 ± 2	13 ± 2

I = intact side, S = sympathotomized side. $n = 8$. The reduction after ICP_e was statistically significant ($P < 0.001$, ANOVA). No statistically significant effect of naloxone was observed. Values given in $g\,min^{-1}\,100\,g^{-1}$ tissue.

ICP_e and MAP was increased due to the central ischaemic response. Naloxone had no marked effect on MAP while TRH caused a marked increase in MAP and thus an increase in CPP. TRH also caused a marked mydriasis on the side with an intact sympathetic supply. No such effect was elicited by naloxone.

Effects of naloxone and elevation of the ICP on the microcirculation

Table 1 presents the local cerebral and spinal cord blood flows before and after ICP_e and after naloxone treatment. There was a marked decrease ($P < 0.001$, ANOVA) in all regional cerebral blood flows after ICP_e. The total CBF decreased by about 70%; see Figure 2. No marked effect of naloxone was observed. However, there were some reductions in rCBF after naloxone, probably due to CPP variations. Consistent significant effects of the sympathotomy on the rCBF were not observed.

The control value for the dural blood flow was 174 ± 31 on the intact side and $188 \pm 46\,g\,min^{-1}\,100\,g^{-1}$ on the sectioned side. The blood flow decreased on the intact side by $86 \pm 2\%$ and by $81 \pm 4\%$ on the sympathotomized side after ICP_e. After elevation of the ICP the decreases for choroid plexuses were $85 \pm 2\%$ and $85 \pm 3\%$ respectively. These decreases were significant at the $P < 0.001$ level (ANOVA). An effect of naloxone treatment was not observed.

Effects of unilateral cervical sympathotomy were clearly seen in some extracranial tissues, e.g. masseter muscle. The baseline blood flow was 16 ± 5 on the intact side and $93 \pm 21\,g\,min^{-1}\,100\,g^{-1}$ on the sympathotomized side. This difference was significant at the $P < 0.01$ level (tested with t test). No clear effect of ICP_e or naloxone treatment was detected.

There was a tendency to an increase in ocular blood flow after ICP_e (Table 3). Prior to this there was a reduced blood flow in all ocular regions on the side with an intact sympathetic supply compared with the sympathotomized side. The difference was statistically significant ($P < 0.05$) in the iris. There was also a tendency to a further increase in blood flow after naloxone administration.

Non cranial organs e.g. heart muscle, duodenum, gastric mucosa, spleen and kidney cortex showed no general pattern of increasing or decreasing blood flow after ICP_e (Figure 3). However, there was a small but statistically significant ($P < 0.05$, SNK) increase in the adrenal gland blood flow. In none of these tissues was there a statistically significant effect of naloxone.

Effects of TRH and elevation of the ICP on the microcirculation

Table 2 gives the local cerebral and spinal cord blood flows before and after ICP_e and after TRH treatment. With a raised ICP there was a similar decrease in all rCBFs as in the experiments with naloxone. The total cerebral blood flow decreased by about 65% (Figure 2). TRH caused a statistically significant increase in almost all regional cerebral blood flows compared

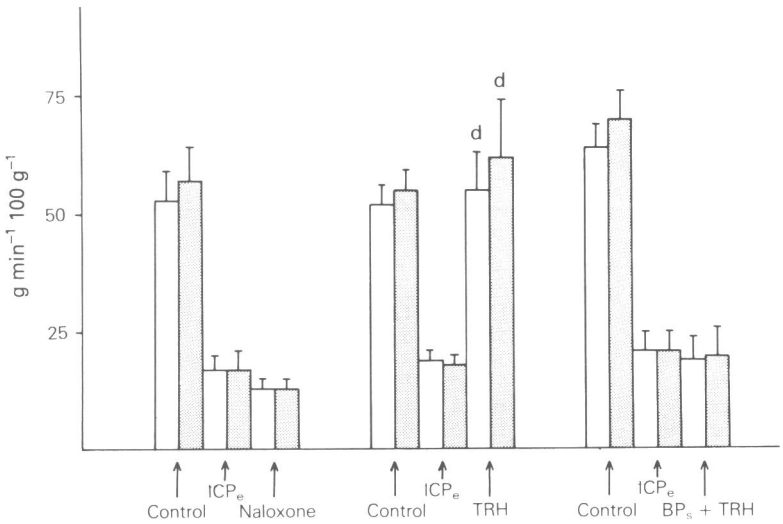

Figure 2 Total cerebral blood flow in control situation, during elevation of the intracranial pressure (ICP_e) and during ICP_e + naloxone ($n = 8$) or TRH ($n = 7$) treatment, and in animals with a normalized blood pressure (BP_s) ($n = 4$). [d] $P < 0.01$ ICP_e values compared with TRH values (SNK test). Values given in $g\,min^{-1}\,100\,g^{-1}$ tissue. Open columns = intact side, shaded columns = sympathotomized side.

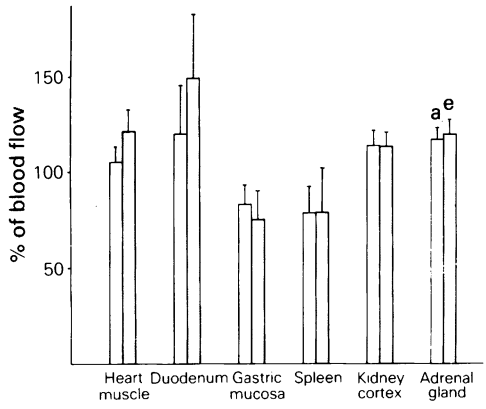

Figure 3 Blood flow as percentage of control values in some peripheral tissues. Open columns = during elevation of the intracranial pressure (ICP_e), shaded columns = during ICP_e + naloxone treatment ($n = 8$). [a] $P < 0.05$ ICP_e values compared with control; [e] $P < 0.05$ naloxone values compared with control (SNK test).

with the blood flow after ICP_e. The rCBF increased almost to control values or even exceeded them. In the cortical grey matter, hippocampal and hypothalamic regions and medulla oblongata flow values after TRH administration were higher on both sides than in the control situation. There was a positive corelation ($r = 0.7215$) between the increase in MAP and the increase in total cerebral blood flow.

In these experiments, control dural blood flow was 177 ± 28 on the intact side and $266 \pm 29\ g\ min^{-1}\ 100\ g^{-1}$ on the sympathotomized side ($P < 0.02$, t test) and decreased by $84 \pm 4\%$ and $83 \pm 2\%$ respectively ($P < 0.001$, ANOVA) after the increase in ICP. After TRH the decrease in flow was $70 \pm 6\%$ on the intact side and $67 \pm 6\%$ on the sectioned side compared with the control value. Thus there was a slight increase in flow compared with ICP values. The decrease for the choroid plexus was $82 \pm 4\%$ on the intact side and $79 \pm 6\%$ on the denervated side ($P < 0.001$, ANOVA). There was an increase in choroid plexus blood flow after TRH administration to $62 \pm 12\%$ of control on the intact side and $50 \pm 11\%$ on the sectioned side respectively.

As in the naloxone experiments the effect of unilateral cervical sympathotomy was evident in the masseter muscle. Control blood flow was 22 ± 8 on the intact side and $69 \pm 20\ g\ min^{-1}\ 100\ g^{-1}$ on the sectioned side. After ICP_e there was a slight decrease to 20 ± 5 on the intact side and a slight increase to $78 \pm 15\ g\ min^{-1}\ 100\ g^{-1}$ on the sympathotomized side. After TRH there was a further decrease to 14 ± 5 on the intact side and an increase to $86 \pm 21\ g\ min^{-1}\ 100\ g^{-1}$ on the sectioned side. The differences between the intact and sympathotomized side were statistically significant ($P < 0.05$), tested with the t test.

The blood flows in the choroid, iris and ciliary processes are given in Table 3. Control blood flows in the choroid and ciliary processes were elevated on the sectioned side as compared with the intact side (P values were < 0.05 and < 0.01 respectively). The same pattern of blood flow changes after ICP_e was observed as in the naloxone experiments. A tendency to an increased blood flow was seen after TRH administration in all ocular blood flows.

Figure 4 shows the percentage blood flow changes in some other organs. Cardiac muscle blood flow was increased ($P < 0.05$, SNK) by TRH in comparision with the ICP value while a statistically significant effect was not found in the kidney cortex or duodenum. As in the naloxone experiments, an in-

Table 2 Regional cerebral and spinal cord blood flows in control situation, after elevation of intracranial pressure (ICP_e) and after ICP_e + TRH

	Control		*ICP_e*		*TRH*	
	I	S	I	S	I	S
Grey matter	47 ± 3	52 ± 5	15 ± 3	15 ± 3	64 ± 16^d	67 ± 19^c
White matter	43 ± 6	44 ± 6	13 ± 2	13 ± 2	40 ± 6^c	44 ± 9^c
Hippocampal region	29 ± 2	29 ± 2	12 ± 1	12 ± 2	39 ± 5^d	53 ± 11^d
Caudate nucleus	66 ± 6	60 ± 6	18 ± 4	19 ± 3	61 ± 8^d	67 ± 9^d
Thalamic region	62 ± 7	66 ± 6	23 ± 3	21 ± 3	65 ± 11^d	77 ± 15^d
Hypothalamic region	48 ± 8	49 ± 9	22 ± 3	19 ± 5	61 ± 12^c	65 ± 17^c
Collicles	66 ± 7	69 ± 5	28 ± 2	28 ± 2	57 ± 9^c	72 ± 14^d
Pons-mesencephalon	58 ± 9	56 ± 8	32 ± 5	30 ± 5	54 ± 8^c	59 ± 8^c
Medulla oblongata	62 ± 14	67 ± 13	37 ± 7	39 ± 11	64 ± 12	71 ± 14
Cerebellum	78 ± 13	79 ± 12	33 ± 7	34 ± 5	69 ± 10	73 ± 10
Spinal cord (C_1–C_3)	52 ± 12	50 ± 11	27 ± 5	23 ± 6	48 ± 10	47 ± 9

I = intact side, S = sympathotomized side. $n = 7$. [c] $P < 0.05$ ICP_e compared with TRH, [d] $P < 0.01$ ICP_e compared with TRH blood flow (SNK test). Values given in $g\ min^{-1}\ 100\ g^{-1}$ tissue.

Table 3 Ocular blood flows in control situation, after elevation of intracranial pressure (ICP_e) and after ICP_e + naloxone ($n = 8$) or TRH ($n = 7$)

	Control		*ICP_e*		*Naloxone*	
	I	S	I	S	I	S
Choroid	1131 ± 284	1285 ± 258	1199 ± 264	1477 ± 286*	1223 ± 233	1448 ± 249
Iris	95 ± 23	121 ± 28*	171 ± 32	254 ± 64	283 ± 58	307 ± 68
Ciliary processes	116 ± 22	162 ± 33	165 ± 15	235 ± 27	208 ± 28	251 ± 32
	Control		ICP_e		TRH	
	I	S	I	S	I	S
Choroid	842 ± 120	1075 ± 98*	1038 ± 217	1270 ± 323	1264 ± 165	1800 ± 213
Iris	58 ± 10	58 ± 10	102 ± 28	162 ± 39	104 ± 21	206 ± 28*
Ciliary processes	95 ± 11	150 ± 17*	113 ± 21	206 ± 42*	137 ± 27	244 ± 40**

I = intact side, S = sympathotomized side. * = $P < 0.05$, ** = $P < 0.01$ comparing intact with sympathotomized side. Values given in mg min^{-1}.

crease in blood flow ($P < 0.01$, SNK) was observed in the adrenal gland after elevation of the ICP. TRH had no effect on this blood flow. However, there was marked decrease in the gastric mucosal and splenic blood flows after TRH administration as compared with the control and ICP_e blood flow ($P < 0.01$, SNK).

Some experiments with blood pressure stabilized animals were performed ($n = 4$). A typical response to TRH was observed with an increase in MAP which was abolished by bleeding into the reservoir. The MAP was 12.0 ± 0.7 kPa in the control situation, 13.5 ± 0.6 kPa after ICP_e and 13.4 ± 0.6 kPa after TRH. Blood (27.5 ± 1.4 ml) had to be removed in order to normalize the blood pressure. The CPP was 2.53 ± 0.25 kPa after ICP_e and 2.40 ± 0.21 kPa after TRH. In Figure 2 the total cerebral blood flow is shown. An effect of TRH was not observed on the total or regional cerebral blood flow.

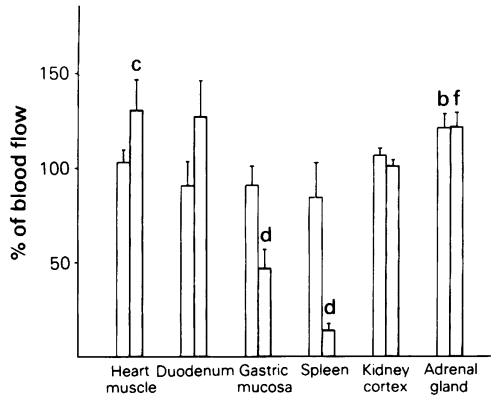

Figure 4 Blood flow as percentage of control values in some peripheral tissues. Open columns = during elevation of the intracranial pressure (ICP_e), shaded columns = ICP_e + TRH treatment ($n = 7$). $^bP < 0.01$ ICP_e values compared with control; $^cP < 0.05$ and $^dP < 0.01$ ICP_e values compared with TRH values; $^fP < 0.01$ TRH values compared with control (SNK test).

Discussion

Increase in the ICP dramatically decreased the rCBF and a cerebral ischaemic response was elicited. TRH caused a further increase in MAP and a normalization of the rCBF. In some peripheral organs a marked vasoconstriction was observed after TRH administration. Naloxone had no marked effects on MAP, rCBF or peripheral blood flow.

The cerebral ischaemia model used in this study has previously been used by Sadoshima *et al.*, (1981). The decrease in rCBF observed in the present study is in good agreement with their results. The cervical sympathetic activity was reported to increase in cerebral ischaemia but a difference in cerebral blood flow between the intact and denervated sides was not detected. Neither was there any appreciable effect of cervical sympathotomy on the cerebral circulation.

TRH caused a marked increase in MAP and CPP and increased cerebral blood flow to control values. TRH is known to cause cerebral vasodilatation (Koskinen & Bill, 1984) and thus might increase CBF both by dilating the cerebral vessels and increasing the CPP. When TRH was administered to animals with cerebral ischaemia and with a stabilized blood pressure, an increase in rCBF was not observed. This observation indicates that under these conditions the dilatation of the cerebral vessels was nearly maximal already before the administration of TRH and that the most important effect of TRH in the other experiments was to increase CPP. Indeed, there was a positive correlation

between the increase in MAP and the increase in total cerebral blood flow. Furthermore, Tuor & Farror (1984) recently reported a passive relationship between CBF and CPP in this CPP range in rabbits anaesthetized with urethane.

In our study naloxone had no significant effect on the rCBF. Conflicting results of naloxone on neurological deficits and cerebral blood flow in cerebral ischaemia have been reported. A reversal of neurological deficit has been shown in the cat, baboon, gerbil and man (Baskin & Hosobuchi, 1981; Levy *et al.*, 1982; Baskin *et al.*, 1982; Hosobuchi *et al.*, 1982). Other reports are controversial indicating no effect in the gerbil (Holaday & D'Amato, 1982; Kastin *et al.*, 1982). The cortical CBF was decreased in the cat ischaemic hemisphere whereas no effect was found in baboon and man after administration of naloxone (Levy *et al.*, 1982; Baskin & Hosobuchi, 1981; Baskin *et al.*, 1982). Our results indicate that opioid mechanisms sensitive to naloxone are unlikely to play a major role in the regulation of the rCBF in cerebral ischaemia due to increased ICP.

The normal dural blood flow reported by Linder (1982) was $41 \pm 8\,g\,min^{-1}\,100\,g^{-1}$ on the side with a deprived sympathetic supply. The control dural blood flow found here was much higher and may well have been due to trauma to the dura. Whether this effect was elicited by a neural mechanism or was due to a direct release of vasodilator substances remains to be clarified.

It is assumed that β-endorphin contributes to the hypotension developed in several shock situations and naloxone seems to counteract this. TRH has been shown to have similar effects to naloxone, although there are some dissimilarities. Blood pressure effects of naloxone in various cerebral ischaemia models have not been detected (Baskin & Hosobuchi, 1981; Levy *et al.*, 1982; Baskin *et al.*, 1982). In our study we also failed to observe any effect of naloxone on the blood pressure. It thus seems likely that the pressor response to naloxone in other ischaemic shock situations e.g. spinal contusion shock, is dependent on the hypotension developed (Faden *et al.*, 1982b). On the other hand, TRH had a marked pressor effect producing an increase in the CPP. We have previously shown (Koskinen & Bill, 1984) that TRH causes an increase in peripheral resistance which is due at least in part to an activation of the sympathetic system which explains the increase in MAP. Whether the activation is elicited in the brain stem, spinal cord or elsewhere is not clear. Indeed, it is known that TRH is widely distributed in the CNS (Hökfelt *et al.*, 1975a, b). There is previous evidence that TRH may cause activation at several levels (Backman & Henry, 1984; Koskinen & Bill, 1984; unpublished results).

Endorphins have been found to be localized in the superior cervical ganglion (Schulzberg *et al.*, 1979) and in the intermediolateral nucleus of the spinal cord (Romagnano & Hamill, 1984) and an effect on the sympathetic system has been postulated (Konishi *et al.*, 1979; 1981). We found no clear evidence for an effect of naloxone on the sympathetic system influencing cerebral or peripheral blood flows.

TRH caused a marked mydriasis on the side with an intact sympathetic supply, whereas naloxone had no such effect. We have shown previously that TRH can induce an increase in the activity in some of the sympathetic fibres to the head (Koskinen & Bill, 1984); such activation explains the effect on the pupil.

There seems to be a sympathetic vasoconstrictor tone to the eye in rabbits under urethane anaesthesia (Koskinen & Bill, 1984.). This tone was not apparently affected by the rise in ICP; the flow increased on both sides. Using pooled data ($n = 15$) there proved to be a statistically significant (t test) increase in the blood flow in the iris from 76 ± 14 to $137 \pm 24\,mg\,min^{-1}$ ($P < 0.01$) on the intact side and from 89 ± 18 to $208 \pm 40\,mg\,min^{-1}$ ($P < 0.01$) on the sectioned side. A similar increase was seen in the ciliary processes; corresponding values were 106 ± 12 to $139 \pm 14\,mg\,min^{-1}$ ($P < 0.05$) on the intact side and 156 ± 19 to $220 \pm 25\,mg\,min^{-1}$ ($P < 0.01$) on the sectioned side. The uveal blood flow is poorly autoregulated and the increase is thus explained by the increase in MAP.

After administration of TRH there seemed to be a further increase in ocular blood flow. TRH has been shown to increase the blood flow slightly, particularly on the side with an interrupted sympathetic supply (Koskinen & Bill, 1984). Thus TRH seemed to activate some of the sympathetic fibres to the eye resulting in a mydriasis without any pronounced vasoconstrictor effect in the eye.

In the present study no consistent effects on blood flow in peripheral tissues were detected after ICP_e. An exception was the adrenal gland where an increase was observed, probably as a part of the central ischaemic response. We found no clear effect of naloxone on peripheral blood flow while TRH caused marked vasoconstriction in the gastric mucosa and spleen. From a previous study it is known that naloxone does not influence the gastrointestinal blood flow whereas an exogenously administered opiate decreased the duodenal blood flow in unanaesthetized rabbits (Koskinen & Bill, 1983). TRH on the other hand has been shown to have marked vasoconstrictor effects on several peripheral tissues (Koskinen & Bill, 1984). Thus the stressful situation in cerebral ischaemia seemed not to influence the blood flow markedly in these tissues nor did opiate receptors sensitive to naloxone contribute to the blood flow pattern of the gastrointestinal tract. TRH on the other hand elicited a marked vasoconstriction, probably due to an activation of parts of the sympathetic system.

In conclusion, a high intracranial pressure markedly

decreased the cerebral blood flow while an increase was observed in the eye and adrenals. Treatment with an μ-receptor antagonist, naloxone, had no effect on blood pressure or rCBF. TRH caused a rise in blood pressure and normalized cerebral blood flow, and reduced flow in several tissues most probably due to a sympathetic activation.

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