CEREBRAL BLOOD FLOW IN RATS AFTER TREATMENT WITH THE PRIMARY SENSORY NEUROTOXIN CAPSAICIN

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ABBREVIATIONS USED

CBF	cerebral blood flow
CCK-8	cholecystokinin
CGRP	calcitonin gene related peptide
CMR-glucose	cerebral metabolic rate for glucose
CMR-O_2	cerebral metabolic rate for oxygen
CVR	cerebrovascular resistance
DMSO	dimethyl sulfoxide
HCO_3^-	bicarbonate ion
ICP	intracranial pressure
IU/ml	international units/ml (concentration)
MABP	mean arterial blood pressure
μg	micrograms (mass)
μl	microlitres (volume)
ml	millilitres (volume)
mM	milli Molar (concentration)
mmHg	millimetres mercury (pressure)
N_2O	nitrous oxide
ngm	nanograms (mass)
NPY	neuropeptide Y
$PaCO_2$	arterial carbon dioxide partial pressure
PaO_2	arterial oxygen partial pressure
$t_{1/2}$	half life
T°C	temperature in degress celcius
TWEEN	polyoxyethelene-sorbitan mono-oleate (TWEEN-80)
VIP	vasoactive intestinal polypeptide

LIST OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

SUMMARY

Cerebral blood flow (CBF) is tightly coupled to the metabolic demands of the cerebral tissue. Understanding of the mechanisms by which CBF is regulated is incomplete. Several neuronal systems innervate cerebral arteries and veins. These include primary sensory peptidergic, cholinergic and sympathetic systems. The primary sensory innervation contains a number of peptides including substance P. Axons containing substance P are found close to the adventitia of the larger cerebral arteries as well as the pial arteries in several mammalian species. The larger cerebral vessels of the frontal cortex are supplied from the ipsilateral trigeminal ganglion. Neuropeptides contained in this primary sensory innervation are depleted by the neurotoxin capsaicin or by trigeminal ganglionectomy. The presence of other vasodilator fibres has made study of this system difficult.

This study sought to determine whether the peptidergic innervation of the cerebral vasculature plays any functional role in the responsiveness of the vasculature to physiological stimuli. Capsaicin is a neurotoxin with a specific target neuron and a well documented effect on the peptide levels of primary sensory unmyelinated nerves. CBF can be measured repeatedly using the hydrogen clearance technique which employs small platinum electrodes. The electrodes cause little damage to brain.

In the first series of experiments, rats were pre-treated with either capsaicin (an agent which depletes peptide from primary sensory neurons) or with cysteamine (an agent which depletes

somatostatin). The responsiveness of the cerebral vasculature was assessed by measuring (CBF) by the method of hydrogen clearance at hyper- normo- and hypo-carbia. Other parameters such as blood pressure, pH and PaO_2 which affect the CBF were kept constant. The efficacy of peptide depletion was assessed by radioimmunoassay of brain microvessel sonicates and whole brain homogenates. By depleting substance P, a vasodilator in many vascular beds, including the brain, it was expected that the response of the cerebral vasculature to circulating $PaCO_2$ would be attenuated. However, resting CBF was increased and the responsivness of the vasculature to $PaCO_2$ was enhanced after capsaicin treatment. These effects do not appear to be related to changes in cerebral metabolic rate nor was there any vascular degeneration. Substance P levels in the cerebral microvessels were not altered by capsaicin treatment although the levels of substance P in whole brain were reduced. Since somatostatin is a release inhibitor, depletion was expected to increase sensitivity to $PaCO_2$. Pretreatment with cysteamine increased CBF at hypocarbia, but not at normocarbia or hypercarbia. Cysteamine reduced somatostatin concentration in whole brain but had no effect on cerebral vessels.

In the second series of experiments, rats were treated with a single dose of capsaicin injected into the right trigeminal ganglion. Changes in steady state CBF were measured by hydrogen clearance. Parameters such as $PaCO_2$, mean arterial blood pressure (MABP), pH and PaO_2 were kept constant. The peptide depletion profile was assessed by radioimmunoassay of left and right trigeminal ganglia. Acute treatment with capsaicin was expected to stimulate substance P release from neuron terminals

of the ganglion, provide a vasodilator stimulus and so increase CBF. However, a vehicle containing dimethyl sulfoxide/saline (DMSO) by itself caused a marked reduction in steady state CBF. Capsaicin administered in this vehicle reversed the vasoconstriction, CBF levels remaining normal throughout the experimental period. If capsaicin was administered in a vehicle containing TWEEN/saline no changes in CBF were found. TWEEN/saline by itself caused no changes in CBF.

The experiments reported here provide evidence for the involvement of primary sensory mechanisms in the regulation of CBF. The data demonstrate that the trigeminal ganglion sensory projection to the cerebral vessels has a functional role in the regulation of CBF. Other capsaicin sensitive neuropeptides could be studied and interspecies differences should also be investigated. It would be possible to repeat this series in awake animals and obviate the difficulties interpreting data from an anesthetised model.

DECLARATION

I certify that this thesis does not incorporate, without acknowledgement, any material previously submitted for a degree or diploma in any University and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Stephen Helps, 1988.

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