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### Title

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### Permalink

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### Journal

Journal of the Neurological Sciences, 19(4)

### ISSN

0022-510X

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### Publication Date

1973-08-01

### DOI

10.1016/0022-510x(73)90039-7

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Peer reviewed

## The Regulation of Regional Blood Flow in the Brain by Visual Input

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(Received 9 February, 1973)

### INTRODUCTION

Cerebral tissue has a requirement for a continuous and rich supply of glucose and oxygen. The delivery of these to precise locations within the brain depends on the cerebral circulation. Even minor or transient variations in the supply of blood-borne nutrients to specific areas of the brain may have a significant effect on their development and function.

We have previously shown that visual deprivation may modify the velocity of blood flow through brain areas directly or secondarily related to visual function (Bondy and Morelos 1971). These changes appear to be widespread and reversible (Bondy and Davis 1972).

We are now reporting data concerned with the speed with which the cerebral circulation can be modified by variations of visual input. The relation of these modifications to changes of light intensity and to pattern deprivation has also been examined. In addition, evidence is presented suggesting that direct neurogenic control may be more important in the regulation of cerebral blood flow than has previously been thought.

The experimental animal used was the chick. The advantages of studying blood flow within the avian brain can be summarized:

(1) The complete decussation of the avian optic tract in conjunction with the absence of major interhemispheric commissures reduces the interactions between the two halves of the brain (Cowan, Adamson and Powell 1961; Levine 1952).

(2) Metabolic deficits caused by monocular visual deprivation are largely confined to regions contralateral to the treated eye (Bondy and Margolis 1969).

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This research was supported in part from National Institutes of Health Grant No. NS09603, and the Foundations' Fund for Research in Psychiatry, Grant No. 70-487.

The author is recipient of National Institutes of Health Research Career Development Award No. 1K04 NS 49945.

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(3) The avian brain is symmetrical with no significant left or right dominance (Levine 1945).

(4) Regions of the brain that receive primary or secondary innervation from the treated eye can be compared to the corresponding regions in the same animal that receive such innervation from the normal untreated eye. Differences observed between pairs of left and right experimental and control regions must be directly caused by the experimental procedure and cannot be attributed to systemic circulatory variations.

(5) The comparison of blood flow within paired regions of a single animal rather than between separate animals enables significant but small variations in flow rate to be detected.

#### MATERIAL AND METHODS

Cerebral blood flow in White Leghorn chicks was determined after a variety of experimental treatments. Groups of 8 chicks were given an intracardiac injection of 19–38  $\mu\text{Ci}$  [ $4\text{-}^{125}\text{I}$ ] iodoantipyrine in 0.1 ml isotonic saline (0.14 M NaCl). Ten sec after this injection, birds were decapitated and individual left and right cerebral hemispheres and optic lobes were dissected out on ice. The thalamic midbrain region was also removed and divided longitudinally into left and right halves. All regions were then weighed and placed in glass scintillation vials together with 10 ml of a xylene-based liquid scintillation solution (Aquasol, New England Nuclear Corp., Boston, Mass.). This solution is miscible with both water and iodoantipyrine. After allowing 24 hr for the isotope to diffuse into this solution, samples were assayed for radioactivity. Efficiency of counting of  $^{125}\text{I}$  was over 88% under these conditions. Radioactivity per unit net weight tissue was calculated and taken as an index of relative blood flow. Iodoantipyrine has been shown to reach a stable level in the brain of rats within 6 sec after injection and to maintain this level for over 1 min (Sapirstein 1958). This compound has been previously used to estimate the relative distribution of cerebral output to paired brain regions (Bondy and Morelos 1971). The ratios of blood flow values for regions contralateral to and innervated by the untreated eye ("visual" areas V) relative to the corresponding regions contralateral to the treated eye ("deprived" areas D), were calculated. To avoid the danger of skewing data, the logarithm of this ratio V/D was taken and the probability of this logarithmic ratio deviating significantly from 0.0 was calculated using Student's one tailed *t*-test.  $P < 0.05$  was taken as significant. Data are thus presented as  $\log V/D \pm$  standard error. Catecholamine assays were carried out by the method of Maickel, Cox, Saillant and Miller (1968).

#### RESULTS

##### *(A) Rapidity of Response of Cerebral Blood Flow to Changes in Visual Input*

###### *(1) Effect of eyelid suture*

New-hatched chicks were monocularly sutured and blood flow through cerebral regions studied after various times. Significant deficits in the rate of blood flow through all regions contralateral to the occluded eye were apparent after 1 hr of suture while no

TABLE 1  
EFFECT OF SHORT PERIODS OF MONOCULAR SUTURE ON BLOOD FLOW IN CEREBRAL REGIONS

Chick age (days)	Duration of suture (min)	Log $\left[ \frac{\text{flow in region contralateral to sutured eye}}{\text{flow in region ipsilateral to treated eye}} \right]$		
		optic lobe	cerebral hemisphere	thalamus
1-2	5	-0.02 ± 0.02	+0.007 ± 0.02	-0.005 ± 0.02
	15	-0.05 ± 0.02 <sup>a</sup>	-0.03 ± 0.02	-0.02 ± 0.007 <sup>a</sup>
	60	-0.18 ± 0.04 <sup>a</sup>	-0.04 ± 0.01 <sup>a</sup>	-0.02 ± 0.01 <sup>a</sup>
15	15	-0.01 ± 0.001 <sup>a</sup>	-0.005 ± 0.001 <sup>a</sup>	-0.015 ± 0.002 <sup>a</sup>

<sup>a</sup>*P* < 0.05.

such asymmetry could be detected after 5 min (Table 1). This suggested that the effect was dependent on a relatively prolonged differential of nervous input and that blood flow through major brain areas is not responsive to transient fluctuations of neuronal activity. At 15 min after suture, there was a reduced blood flow in optic lobes and thalamic regions contralateral to the closed eye but no statistically significant asymmetry was seen in the cerebral hemispheres. The optic lobe and several thalamic regions such as the lateral geniculate and the ectomammillary nuclei, receive direct innervation from the retinal ganglion cells of the eye. However, the cerebral hemisphere is only indirectly innervated from the eye. This may explain the longer time of eyelid suture required to modify the rate of blood flow through the cerebral hemisphere. Fifteen min of eyelid suture of older birds (15 days after hatch) resulted in reduced blood flow in all contralateral areas studied (Table 1). The adaptability of the cerebrovascular system to varying visual input appears to be retained and perhaps increased during brain maturation.

(2) *Effect of sudden exposure to patterned light*

Both eyes of chicks were sewed shut immediately at hatch and after 1 hr, a single eye was opened. Cerebral blood flow was higher in all regions contralateral to the newly-opened eye, within 5 min and also at 20 min (Table 2). Changes in blood flow appeared more rapidly following exposure to patterned light rather than after patterned light removal. If both eyes were kept sutured for 7 days before reopening one eye, blood flow in the optic lobes and thalamic regions contralateral to the opened eye, was increased 20 min after suture removal. However, at this time there was no such increase found in the contralateral cerebral hemisphere. If this latter experiment were carried out on week-old birds, both eyes being sewed shut for a further week, a significant circulatory response was seen in all regions 20 min after re-opening a single eye. This again suggests that the cerebrovascular system of the more mature brain may possess a more rapid flexibility to varying visual input.

(B) *Blood Flow Regulation by Intensity or by Information Content of Light*

In order to distinguish between the intensity and information quality of light reaching the retina, 2 experiments designed to partially separate these characteristics were

TABLE 2

RESPONSE OF CEREBRAL CIRCULATION TO EXPOSURE OF A SINGLE EYE TO PATTERNED LIGHT AFTER PERIODS OF BINOCULAR SUTURE

Duration of binocular suture	Time after suture removal from one eye (min)	Log $\left[ \frac{\text{flow in region contralateral to exposed eye}}{\text{flow in region ipsilateral to exposed eye}} \right]$		
		optic lobe	cerebral hemisphere	thalamus
<i>Chick 1-day-old at suture</i>				
1 hr	5	0.10 ± 0.02 <sup>a</sup>	0.06 ± 0.02 <sup>a</sup>	0.04 ± 0.01 <sup>a</sup>
1 hr	20	0.05 ± 0.02 <sup>a</sup>	0.06 ± 0.01 <sup>a</sup>	0.03 ± 0.01 <sup>a</sup>
7 d	20	0.04 ± 0.015 <sup>a</sup>	0.02 ± 0.01	0.03 ± 0.01 <sup>a</sup>
<i>Chick 7-days-old at suture</i>				
7 d	20	0.06 ± 0.01 <sup>a</sup>	0.04 ± 0.01 <sup>a</sup>	0.04 ± 0.01 <sup>a</sup>

<sup>a</sup>  $P < 0.05$ .

carried out. In the first study, an opaque polyvinylchloride film (Parafilm) was taped over the eye. This film removes virtually all pattern content from light passing through it while over 75% of incident light is transmitted. When a single eye of a new-hatched chick was treated in this manner for 1 hr, no difference was seen in the rate of blood flow in left and right cerebral regions (Table 3). Thus, under conditions where light intensity is reduced by around 25%, a major deficit in visual information input does not modify blood flow through primarily or indirectly innervated brain areas. The second treatment was the topical application of a pupillary dilator (10% phenylephrine hydrochloride) to a single chick eye, in the presence of a high level of illumination.

TABLE 3

CEREBRAL BLOOD FLOW 1 HR AFTER MANIPULATION OF VISUAL INPUT TO A SINGLE EYE

Treatment	Log $\left[ \frac{\text{flow in region contralateral to treated eye}}{\text{flow in region ipsilateral to treated eye}} \right]$		
	optic lobe	cerebral hemisphere	thalamus
Parafilm eye-cover	0.02 ± 0.03	0.01 ± 0.02	-0.01 ± 0.01
10% Phenylephrine	0.09 ± 0.03 <sup>a</sup>	0.04 ± 0.03	0.02 ± 0.008 <sup>a</sup>

<sup>a</sup>  $P < 0.05$ .

This increases light falling on the retina while not raising the information content to the eye. One hr after such application of phenylephrine to the eye of a chick maintained within 35 cm of a 200 watt light bulb, there was an increase in blood flow through the contralateral optic lobe and thalamic region (innervated by the treated eye) (Table 3). There was no significant change of blood flow in the cerebral hemispheres. Thus, while light intensity may regulate blood flow in regions directly innervated by the optic nerve, neither pattern deprivation nor changes in illumination intensity alone seem to effect rapid changes in hemispheric blood flow. In this area, a more complex interaction of factors may be involved in modifications of blood flow rate.

*(C) Effect of Pharmacological Agents on Regulation of Cerebral Blood Flow**(1) Excitation and depression*

New-hatched chicks were monocularly sutured and immediately injected intraperitoneally with 0.1 ml solution containing either 1.5 mg of sodium thiopental (which caused the animal to lose consciousness) or 0.8 mg of *d*-amphetamine sulfate (which caused hyperexcitability). To ensure that the unsutured eye received relatively normal light input, thiopental-treated chicks had this eye taped open. After 1 hr, the blood supply to paired brain regions of thiopental-treated chicks, was identical (Table 4). Thus, the blood supply to the brains of these birds was not responsive to varying conditions of illumination. In man thiopental reduces the overall rate of cerebral blood flow but the reactivity of blood vessels to carbon dioxide is maintained (Pierce, Lambertsen, Deutsch, Chase, Linde, Dripps and Price 1962). It may be that the local concentration of carbon dioxide is not the mayor means by which cerebral blood flow is responsive to sensory stimulation. The amphetamine-treated birds showed vascular responses to 1 hr of eyelid suture that were very similar to those of untreated birds (Tables 4 and 1). Thus, this drug did not appear to interfere with normal cerebrovascular regulatory mechanisms.

TABLE 4

EFFECT OF VARIOUS AGENTS ON ABILITY OF REGIONAL BLOOD FLOW TO RESPOND TO 1 HR OF MONOCULAR SUTURE

Details of drug administration are given in the text.

Treatment	Log $\left[ \frac{\text{flow in region contralateral to sutured eye}}{\text{flow in region ipsilateral to sutured eye}} \right]$		
	optic lobe	cerebral hemisphere	thalamus
Thiopental	0.01 ± 0.01	-0.03 ± 0.02	0.002 ± 0.01
Amphetamine	-0.04 ± 0.01 <sup>a</sup>	-0.04 ± 0.01 <sup>a</sup>	-0.02 ± 0.003 <sup>a</sup>
Reserpine	-0.01 ± 0.02	-0.02 ± 0.01	0.004 ± 0.01
8% CO <sub>2</sub>	-0.045 ± 0.02 <sup>a</sup>	-0.04 ± 0.01 <sup>a</sup>	-0.005 ± 0.01

<sup>a</sup> *P* < 0.05.*(2) Neurogenic regulation of cerebral blood flow*

In an attempt to reduce autonomic control of the diameter of cerebral blood vessels, new-hatched chicks were injected intraperitoneally on 3 successive days with 0.083 mg reserpine. This treatment resulted in a 96% reduction of cerebral catecholamine levels from 0.082 µg norepinephrine / g wet brain to 0.003 µg / g wet brain. Three hr after the final reserpine injection, chicks were monocularly sutured and after a further hr, regional blood flow within the brain was examined. There was no asymmetry of flow in any pairs of left and right areas (Table 4). While the chicks were still able to respond behaviourally to light, it is possible that the high dose of reserpine used considerably impaired cerebral synaptic function. Thus, the non-responsiveness of cerebral blood flow may have been due to a direct effect of reserpine on the brain or on nerves within the walls of cerebral blood vessels.

An experiment was carried out in order to see whether regional blood flow could be regulated in the presence of a concentration of CO<sub>2</sub> sufficient to cause near maximal chemical vasodilation. New-hatched chicks were monocularly sutured and at once placed into a chamber where the atmospheric gas composition was maintained at 8.5% CO<sub>2</sub>, 39.8% O<sub>2</sub> and 51.7% N<sub>2</sub>. Blood flow was determined in brain areas after a 30 min exposure to this gas mixture. There was a significant deficit in blood flow through the hemispheres and lobes contralateral to the sutured eye relative to the corresponding ipsilateral regions (Table 4). Thus, cerebral blood vessels are still able to modify blood supply even when they are highly dilated by chemical means. It may be that perivascular adrenergic nerves play a role in this regulation.

#### DISCUSSION

Although the major factor determining cerebral blood flow is the vascular content of CO<sub>2</sub> (Wollman, Alexander and Cohen 1967) and the ability of perivascular innervation to alter cerebral blood flow is generally regarded as minor (Harper, Deshmuk, Rowan and Jennett 1971; Waltz, Yamaguchi and Regli 1971), some evidence does exist for a degree of neurogenic regulation of such flow (Mchedlishvili 1972). Our data suggests that at least in the chick, the autonomic nervous system may significantly effect changes in the velocity of circulation of blood through localised cerebral areas.

The flow of blood through brain regions may be continuously fluctuating in the normal animal. It is likely that smaller, more precisely-defined areas associated with specific functions are subject to greater changes in the blood flow rate than the 5–20% changes reported here. Olesen (1971) has shown a 54% increase of blood flow in the focal area of hand representation within the motor cortex in man during arm work.

Barker (1972) reported that the number of cerebral cells per unit length of capillary diminished from the arterial to the venous end, in rat brain. He suggested diffusion of nutrients may be limiting to cell number in distal segments. Thus, vascular supply during development may be critical in determining the extent of cerebral differentiation. A relation has been found between the vascularity of cerebral areas and the extent of dendritic arborization within those areas (Hough and Wolff 1939). Small reductions of nutrient supply may also lead to selective cell loss in the mature brain and this may be a common form of cerebral impairment (Barker 1972). The cerebrovascular bed of the thiopental- and reserpine-treated chick is unable to respond to changed conditions of illumination. Chronic use of central nervous system depressants could have adverse effects on the development of brain function and on its subsequent maintenance.

If the degree of activity can affect blood flow rate and this in turn determines cell density, the growth and persistence of the efficacy of brain regions may be regulated by a cyclic feedback system where the activity of a region enhances its metabolism, which in turn enables the region to function more effectively. Vascular supply may mediate in the observed relation between environmental complexity and brain cell number and weight (Krech, Rosenzweig and Bennett 1963). Thus, the quality of afferent sensory input may in part determine the extent of post-natal arterial growth which is consi-

derable in man (Harnarine-Singh and Hyde 1970). As fluctuation of blood flow within specific brain areas can be a rapid process, this may in part account for the increased metabolism and changes in several biochemical parameters reported in functionally active brain regions. The supply of oxygen to the cerebral cortex may have a low safety margin and may verge upon insufficiency even in the normal state (Davies and Bronk 1957). While acute, transient anoxic conditions may severely retard brain cell development perhaps by interfering with RNA or protein metabolism (Hicks, Cavanaugh and O'Brien 1962), a more subtle vascular insufficiency may also impair optimal brain function.

#### ACKNOWLEDGEMENTS

The excellent technical assistance of Mr. Fred N. Davis and skilled secretarial help of Mrs. Jane Mitchell is greatly appreciated. Catecholamine assays were kindly carried out by Dr. Antonia Vernadakis and Miss Ann Shriver.

#### SUMMARY

The blood supply to several regions of the chick brain is rapidly decreased following reduction of visual input by monocular eyelid suture. This decrease is not confined to the primary visual area (the optic lobe) contralateral to and innervated by the sutured eye but is also apparent in the indirectly innervated cerebral hemispheres contralateral to the treated eye.

After periods of bilateral eyelid suture, exposure of a single eye to patterned light by suture removal results in a rapid increase of blood flow through contralateral cerebral regions directly or secondarily innervated by the exposed eye. This response appears to be more closely related to the intensity rather than to the information content of incident light.

The ability to regulate regional cerebral blood flow is lost following reduction of brain catecholamine levels with reserpine. However, cerebral blood flow is still responsive to afferent sensory input, in the presence of a concentration of carbon dioxide sufficient to cause near maximal dilatation of cerebral blood vessels. This suggests that variations of vascular supply to specific brain regions may in part be effected by direct autonomic nervous mechanisms regulating the diameter of blood vessels within the brain.

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