SOME MECHANISMS OF THE PATHOGENESIS OF ACUTE DISTURBANCE OF THE CEREBRAL CIRCULATION

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Despite much research into the pathogenesis of acute disturbances of the cerebral circulation, this problem remains inadequately studied. In the course of the study of the clinical aspects of acute disturbances of the cerebral circulation the question of the causes of the discrepancy which often arises between the extent of the clinical picture and the relatively slight disturbance of the circulation is invariably raised.

This discrepancy may have several causes, an important one being the development of spasm in a relatively extensive vascular field, resulting from influences arising from a localized zone of disturbance of the circulation. This hypothesis is based on findings obtained from the study of similar relationships in other vascular fields (the coronary circulation [3], the mesenteric arterial system [1]).

The object of the present investigation was to make an experimental study over a long period of time of the possibility of the development of secondary spasm of the cerebral arteries in the presence of a circumscribed disturbance of the blood flow. We attempted to study the reaction of the vessels and changes in their tone in response to certain humoral stimulants (acetylcholine, adrenalin), to reflex influences from the carotid sinus, to the ganglion-blocking drug hexamethonium, and to partial restriction of the blood flow.

EXPERIMENTAL METHOD

The cerebral circulation was studied by means of flat thermoelectrodes as recommended by M. E. Marshak [4]. The thermoelectric method enables us to study the volume velocity of the blood flow in the pial vessels of the brain. The thermoelectrode was fixed with phosphate cement in a bur hole in the vault of the skull so that the thermocouple was in contact with the pia mater. The dura was first removed. In this way the skull was hermetically sealed and experiments could continue for a long period of time. Changes in the thermoelectric current were recorded with the M-21/4 galvanometer on a photokymograph.

An acute disturbance of the circulation was produced by coagulation of a pial vessel using a thermoelectrode with a diameter of 0.75 mm introduced through the opening, which was closed before and after coagulation. The animals took part in the experiment one week after insertion of the thermoelectrode. The volume velocity of the blood flow was investigated before and immediately after coagulation of the vessel, and daily thereafter until the normal circulation was restored.

The reactions of the cerebral vessels to administration of acetylcholine (5 μg/kg) and adrenalin (4 μg/kg) were assessed by the changes in the volume velocity of the blood flow. Hexamethonium was tested in a dose of 0.005 g/kg body weight. The solution was injected into the auricular vein over 10-15 seconds. The interval between the individual injections was 20-25 minutes. The order of injection of the solutions was strictly observed.

When studying the reflex influences from the carotid sinus zone the common carotid artery was exteriorized in a skin flap on the side opposite to that of the thermoelectrode. The pressure receptors were stimulated by compression of the carotid artery.

Changes in the local circulation were brought about by clamping the common carotid artery, exteriorized in a skin flap on the same side as the thermoelectrode, for 30 seconds.

The investigations were conducted on 10 rabbits; altogether 76 experiments were carried out and 456 reactions were studied.

EXPERIMENTAL RESULTS

In 7 of the 10 experiments, injury to a cerebral vessel by means of pin-point cauterization caused a considerable reduction of the volume velocity of the blood flow in the pial vessels of the brain. In four of these experiments spasm developed and lasted for 1-2 hours, i.e., throughout the experiment, while in 3 experiments vasodilatation supervened after transient spasm. In 2 experiments the reduction in the blood flow was preceded by a temporary (2-6 minutes) increase. A slight exception was the case in which no decrease in the blood flow was observed for an hour after trauma to the vessel.

We gained the impression that the differences in the course of the initial changes were dependent on the degree of injury. The less severe and the more superficial the thermocoagulation, the less the spasm. If the thermocoagulation was done 0.5 mm deeper, the decrease in the volume blood flow was more marked.

Despite slight differences in the course of the initial changes after injury, 24 hours later there was always a decrease in the volume velocity of the blood flow compared with the initial value, and only after 3 or 4 days was the initial blood flow restored. It must be pointed out that in animals after thermocoagulation the level of the blood flow was very unstable even in the absence of stimulation (the "background" blood flow). This was shown on the photokymograph in the form of waves, sometimes with a definite periodicity. Before trauma to the vessel these variations in the level of the blood flow were not observed. Consequently, even slight trauma led to a prolonged change in the tone of the cerebral vessels.

The unstable background blood flow could be observed in the animal 3 months later, but only when the functional load was increased and frequent reflex stimuli were applied to the animal. Moreover, in animals subjected to trauma to the vessel, and apparently recovering completely the initial state of the circulation, irradiation with x-rays again produced the same changes in the blood flow as were observed in the acute period of the disturbance of the cerebral circulation.

In the period of acute disturbance of the circulation the reaction of the functionally modified vessels to reflex influences from the pressure receptors of the carotid sinus was significantly altered. Normally, for instance, stimulation of the pressure receptors caused dilatation of the cerebral vessels (Fig. 1, A). Immediately after coagulation of the vessel, the same stimulation caused a reduction of the blood flow. The vasoconstrictor effect became still more marked after 30 minutes to 1^1_2 hours. Four, and sometimes 24, hours after thermocoagulation of the vessel the reaction was partly restored to normal, and sometimes the vasodilator effect was more marked than in the unaffected vessels. This normalization, however, was only relative and repeated stimulation could again produce the state of spasm of the vessels instead of the vasodilator effect.

These changes mentioned above were also observed in experiments in which thermocoagulation caused a considerable reduction of the volume velocity of the blood flow (suggesting an increase in the tone of the cerebral vessels and, evidently, some degree of spasm), and also in experiments in which thermocoagulation led to an immediate dilatation of the cerebral vessels.

The absence of vasodilator effects in the period when an increase in the blood flow was observed might be described as an adaptive reaction of the cerebral vessels. Mchedlishvili [5] showed that when the pressure in the cerebral veins is raised, spasm is observed in the vessels carrying blood to the brain, thereby protecting the brain against overfilling with blood. However, in animals with a very low velocity of blood flow this vasodilator effect was also absent. This is evidence of a disturbance of the regulatory mechanisms determining the blood flow into the brain. It is evident that an important part in the genesis of these disturbances is played by the reflexogenic zones situated along the intracerebral arteries, and described by Kreindler from morphological observations. Kreindler submits that when the function of such a reflexogenic zone is disturbed, circulatory disturbances arise throughout the territory controlled by this reflexogenic zone. Our results can be regarded as experimental proof of Kreindler's hypothesis.

A circumscribed injury to a vessel may thus cause extensive changes in the tone of the vascular wall, and spasm arises in the affected vascular field. The functionally modified vessels cease to react by dilatation to stimulation from the carotid sinus. The transient restoration of the initial blood flow and of reflex reactions soon after injury and thereafter for 3-7 days suggests that they are dependent on functional disturbances.

Studies of the reaction of the vessels to changes in the local circulation after clamping the common carotid artery for 30 seconds also revealed considerable abnormalities in the presence of a disturbance of the cerebral circulation. Whereas restriction of the blood flow in normal animals caused a comparatively small reduction of the

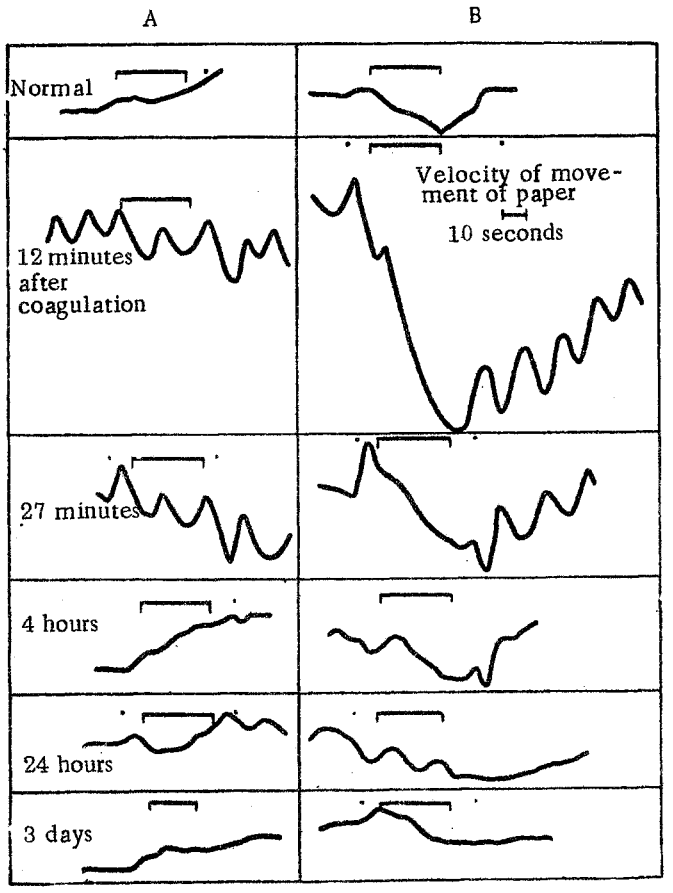

Fig. 1. Changes in the volume velocity of the blood flow in a rabbit. A) During reflex stimulation of the carotid sinus; compression of the common carotid artery on the left side, thermoelectrode on the right; B) after exclusion of one common carotid artery; clamping of the artery on the same side as the electrode.

blood flow, in animals after trauma to a cerebral vessel the blood flow was very considerably reduced (Fig. 1,B). The increased sensitivity of the cerebral vessels to changes in the circulatory conditions was especially marked immediately after injury, and also within the first few hours thereafter. Full restoration of the reaction to its original magnitude was not observed during the subsequent 1-3 days. Some degree of normalization later ensued.

Arterio-arterial and veno-venous anastomoses are known to be present on the brain surface [2]. Injury to any vessel brings into play a collateral circulation and usually has no significant effect on the blood supply to the brain tissue in the region of the injured vessel. This rich anastomosis of vessels enables the circulation in the systems of the cerebral vessels to be equalized rapidly, as shown by the comparatively small reduction in the volume velocity of the blood flow after exclusion of one carotid artery in normal animals. An important role in this adaptive reaction is played by the chemoreceptors, which are extremely sensitive to a fall in the supply of oxygen. Stimulation of the chemoreceptors leads to vasodilatation and to the inclusion of nonfunctioning capillaries, which also increases the volume velocity of the blood flow. In the opinion of several workers, the principal factor controlling the blood flow through the collaterals is the pressure within the vessel. Consequently, a decrease in pressure during the temporary exclusion of one of the four arteries supplying the brain must also cause the collateral circulation to come into play. However, all the mechanisms responsible for restoring the circulation and regulating the flow of blood into the brain are modified during the period of acute disturbance of the cerebral circulation, and hence the disturbed circulation is not restored and reactions of a vasoconstrictor character prevail.

The study of the effect of the ganglion-blocking drug hexamethonium on the cerebral circulation showed that, on the cessation of influences from the autonomic divisions of the nervous system, a more marked spasm was present

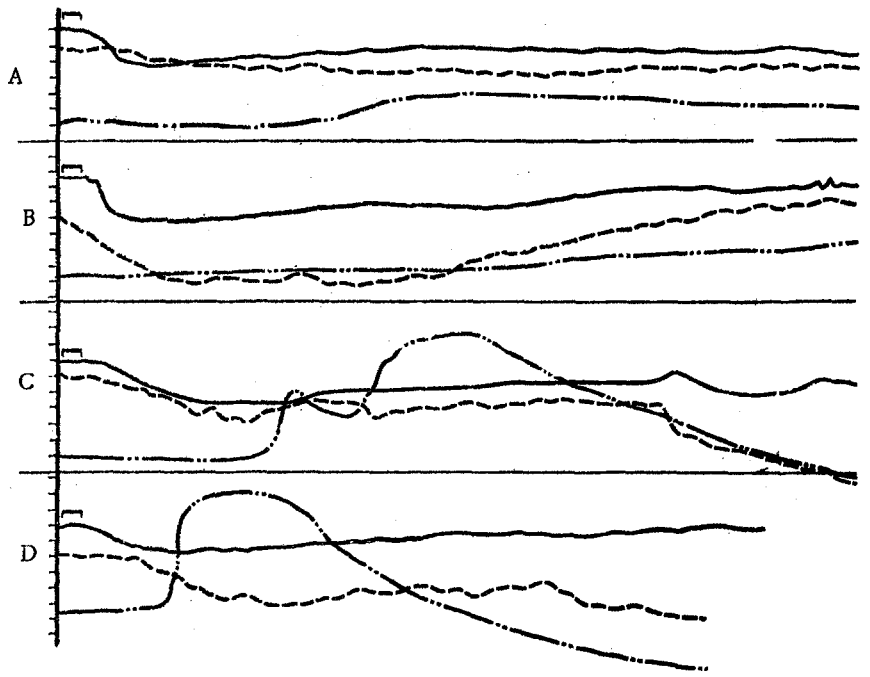

Fig. 2. Changes in the arterial pressure (—), volume velocity of the blood flow (— — —) and the peripheral vessels as shown by changes in the temperature of the ear (— •• —) in an animal in normal conditions and in a period of acute disturbance of the cerebral circulation after administration of hexamethonium. A) In normal conditions; B) immediately after cauterization; C) 24 hours later; D) 2 days after cauterization.

in the cerebral vessels of the animals with a disturbed cerebral circulation with the same degree of lowering of the general arterial pressure (Fig. 2). The reduction in the blood flow was especially great if hexamethonium was given during the first minutes after the onset of acute disturbances of the cerebral blood flow. Full restoration of the initial magnitude of the reaction was not observed for 2-3 days. With the re-establishment of the cerebral hemodynamics the reaction of the cerebral vessels approximated to its original magnitude. This series of experiments indicates a strengthening of the tonic influences from the local regulatory systems situated in the vascular formations of the brain themselves, for central influences were excluded by the administration of hexamethonium.

The intravenous injection of substances closely related to the mediators of nervous excitation showed that the sensitivity of the cerebral arteries in acute disturbances of the cerebral circulation undergoes considerable modification. For instance, whereas the intravenous injections of acetylcholine into normal animals initially caused a small, transient reduction in the volume velocity of the blood flow in the brain, followed by an equally small increase in the flow, in animals after trauma to a cerebral vessel the reaction was modified. Immediately after thermocoagulation of the vessel, acetylcholine caused a marked spasm of the cerebral vessels, and no phase of dilation was observed. After 24-48 hours the reaction approximated to its initial form, although the increase in the blood flow was less than in the normal animals.

Changes in the reaction of the cerebral vessels were also observed after injection of adrenalin. In normal animals adrenalin caused a small increase in the blood flow, which was not due to an increase in the general arterial pressure because adrenalin produced a rise of pressure for only 3 minutes, while the increase in the blood flow lasted much longer. After thermocoagulation the blood flow was increased only during the period of elevation of the arterial pressure, after which it fell below the original level. Subsequently a gradual restoration of the reaction took place.

The results demonstrate that during an acute disturbance of the blood flow the mechanism of neuro-humoral regulation is modified.

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