LOCUS COERULEUS: REGULATION OF BLOOD-BRAIN BARRIER FUNCTION IN NORMAL AND EMOTIONALLY STRESSED RATS

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Emotional stress induced by single long-term immobilization leads to disturbances of the blood-brain barrier (BBB). Increased permeability of BBB in the medullary reticular formation is associated with widening of the spaces between adjacent endothelial cells, whereas in the mesencephalic reticular formation the vessel walls are ruptured [2, 3].

Adrenergic endings have been found on the walls of intracerebral vessels, including small arterioles and capillaries. Some of them are axon endings of neurons in the superior cervical ganglia. Recently, however, evidence has been obtained that the locus coeruleus plays an important role in the adrenergic innervation of vessels in the brain parenchyma [8, 10, 11].

In the investigation described below the role of the principal noradrenergic nucleus of the brain in the regulation of BBB function in normal and emotionally stressed rats was investigated with the aid of a specific blocker of the locus coeruleus.

EXPERIMENTAL METHOD

Experiments were carried out on male Sprague-Dawley rats weighing 150-175 g. The rats (n = 21) were given intraperitoneal injections of DSP4 (N-2-chloroethyl-N-ethyl-2-bromobenzylamine) in a dose of 50 mg/kg body weight in physiological saline. Rats of the control group were divided into subgroups: nine rats received injections of physiological saline, three rats received no injections. After 1 week the rats were lightly anesthetized with ether and a polyethylene catheter was introduced into the abdominal aorta; the free end of the catheter was exteriorized on the dorsal surface of the neck and secured with adhesive tape.

The rats were immobilized 2 days after catheterization, with their limbs and head securely fixed [9]. The blood pressure (BP) was recorded on a "Grass" polygraph immediately before immobilization, in the resting state, and every hour during the experiment.

An intravenous injection of Evans' blue (20 mg/kg in 0.5 ml of 0.14 M NaCl) was given to the rats 6.5 h after immobilization. The animals were decapitated 30 sec after the injection and the brain quickly removed, frozen in liquid propane, and processed by the Falck–Hillarp method.

EXPERIMENTAL RESULTS

Animals receiving DSP4 were indistinguishable from the controls before insertion of the catheter. After catheterization the rats became weak, ate virtually no food, and lost 20-30 g in weight during the two postoperative days. Some animals died in the postoperative period.

Definite lesions of the vessel walls were found in all parts of the brain parenchyma. The lesions were located mainly in the neocortex (in its anterior zones), hypothalamus, and brain stem: in the mesencephalic and medullary reticular formation (RF) (Fig. 1).

Traces of hemorrhages, damaged vessel walls, and extravasation of Evans' blue–plasma protein complex, giving red fluorescence, were observed.

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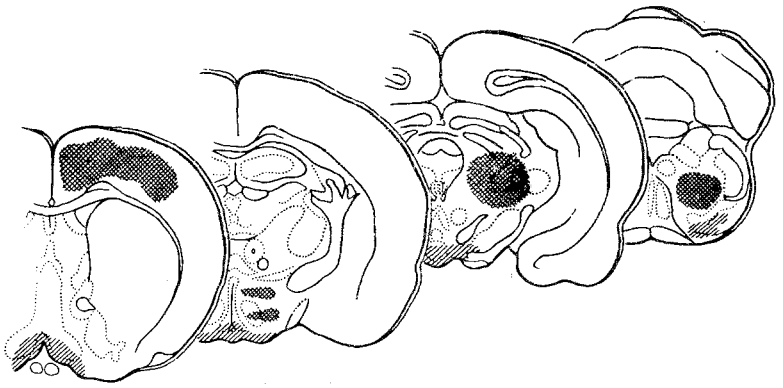

Fig. 1. Diagram showing predominant locations of lesions of cerebral blood vessels after blockage of locus coeruleus by DSP4.

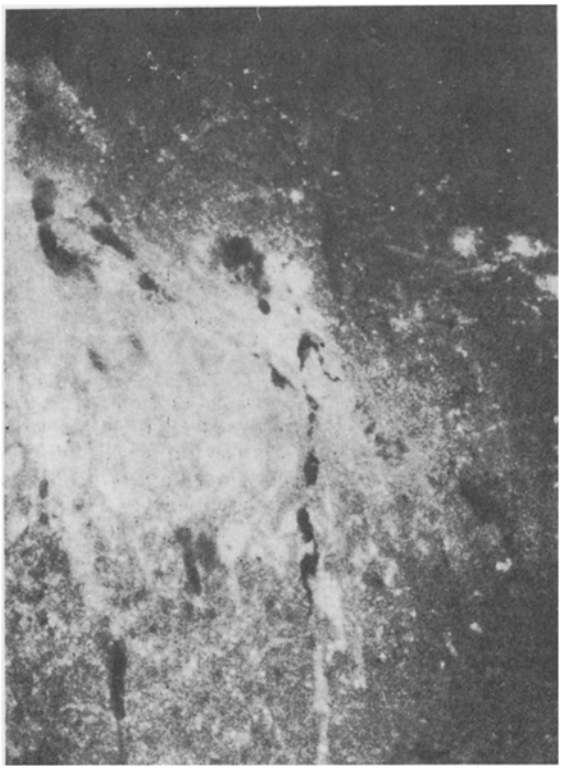

Fig. 2. Hemorrhage into locus coeruleus of rat after immobilization preceded by injection of DSP4. Evans' blue. Falck–Hillarp method. 140 ×.

In addition, hemorrhages were observed into the locus coeruleus and nucleus subcoeruleus of all animals receiving DSP4, resulting in loss of neurons of these nuclei (Fig. 2).

DSP4 is considered to be a specific blocker of nerve endings of neurons located in the locus coeruleus [4-7, 12]. Injection of DSP4 initially causes degeneration of both central and peripheral noradrenergic fibers. However, the peripheral adrenergic plexuses soon (in the course of 1 week) recover. Noradrenergic terminals in the cerebral and cerebellar cortex do not reacquire their original appearance until 6 months after injection of DSP4.

These observations, and also the fact that in the present experiments injection of DSP4 induced hemorrhage into the locus coeruleus and nucleus subcoeruleus, with loss of neurons contained in them, suggest that the vascular lesions and the resulting damage to the brain parenchyma discovered in this investigation were the result of abolition or of drastic weakening of central noradrenergic regulation of BBB function.

As was pointed out above, animals receiving DSP4 began to differ appreciably from the control animals, after implantation of the catheter for direct measurement of BP, by their general weakness, loss of body weight, and in some cases, death of the rats. Implantation of the catheter can be regarded as surgical stress which, against the background of damage to the locus coeruleus, caused these severe morphological and behavioral changes in the animals.

During immobilization of rats previously treated with DSP4 the trend of BP was different. In two animals of those investigated morphologically the initially high BP level (160 mm Hg) remained virtually unchanged until the end of the experiment. In two other animals BP fluctuated considerably during immobilization, and at the end of the experiment it had fallen by 30-40 mm Hg compared with the initial level. In four rats BP remained at virtually the original level throughout the experiment.

In all cases substantial lesions of the blood vessels and brain tissue were found. Other features of the animals receiving DSP4 and immobilized were a decrease in the intensity of fluorescence of adrenergic endings in the vessel walls of the pia mater and meningeal hemorrhages.

The specific nature of the trend of BP during immobilization was reflected to only a comparatively limited degree on the state of the vessels and brain tissue: The lesions were considerable in all cases. Only in the ventral zone of the pons and medulla were the lesions of the vessels and brain tissue appreciably more marked in rats with an initially high BP and in rats whose BP fell sharply during immobilization.

Thus, both surgical and, in particular, long-term emotional stress, preceded by destruction of the locus coeruleus, causes severe damage to the brain vessels and, in turn, this causes destruction of nerve and glial cells.

It can be concluded from the results of this investigation that the locus coeruleus, the principal noradrenalin-synthesizing brain nucleus, plays a decisive role in maintaining the integrity of BBB. The results thus agree with earlier views regarding the homeostatic function of the locus coeruleus, which is manifested particularly dramatically during stress [1].

LITERATURE CITED

1. T. I. Belova, E. L. Golubeva, and K. V. Sudakov, Homeostatic Functions of the Locus Coeruleus [in Russian], Moscow (1980).
2. T. I. Belova and J. Jonsson, Byull. Eksp. Biol. Med., 96, 3 (1983).
3. T. I. Belova and J. Jonsson, Acta Physiol. Scand., 116, 21 (1982).
4. J. Jonsson, Ann. Rev. Neurosci., 3, 169 (1980).
5. J. Jonsson and H. Hallman, Neurosci. Lett., 9, 27 (1978).
6. J. Jonsson, H. Hallman, F. Ponzio, and S. Ross, Eur. J. Pharmacol., 72, 173 (1981).
7. J. Jonsson, H. Hallman, and E. Sundström, Neuroscience, 7, 2895 (1982).
8. S. I. Harik and T. McGunigal, Ann. Soc. Neursci., 9, Abst. No. 4912 (1983).
9. R. Kvetnansky and L. Mikulaj, Endocrinology, 87, 738 (1970).
10. J. A. Nathanson, TINS, 6, 422 (1983).
11. S. J. Peroutka, M. A. Moskowitz, J. F. Reinhard, and S. H. Snyder, Science, 208, 610 (1980).
12. S. B. Ross, Brit. J. Pharmacol., 58, 521 (1976).