Effect of Large Mesencephalic-Diencephalic Lesions on the Noradrenalin, Dopamine and 5-Hydroxytryptamine Neurons of the Central Nervous System

There exist large ascending noradrenalin (NA), dopamine (DA) and 5-hydroxytryptamine (5-HT) neuron systems to the telencephalon and diencephalon[1]. For several purposes it would be of value to interrupt these systems. Since practically all of them run fairly close together in the medial ventral area of the cranial part of the mesencephalon, large lesions have been made in this region in the present study.

In about 70 male Sprague-Dawley rats (body weight 300–400 g) large electrolytic lesions[2] were made medially in the border zone between the mesencephalon and diencephalon. After operation the rats were fed by stomach tube daily. They were kept at a temperature of 27 °C. The rats were killed 3–60 days after operation, most of them being killed after about 14 days. Untreated rats of the same strain and weight served as controls. A little more than half of the rats were taken for biochemical determinations of NA, DA and 5-HT[3–8]. The diencephalon plus the mesencephalon of these animals were placed in 10% formalin, embedded in paraffin, sectioned, stained with toluidine blue, and the site of the lesion examined under a light microscope. The brains of the rest of the animals were taken for examination by the histochemical fluorescence method for NA, DA and 5-HT[9,10]. (For practical details, see [11].) In some cases also the spinal cord was analysed biochemically and histochemically.

The position of a typical lesion is shown in Figure 1. It was usually symmetrical and involved the midline structures of the cranial third of the mesencephalon and the caudal third of the diencephalon, leaving only the lateral third of these regions intact. Animals with lesions of this type displayed the following signs: hunched-back posture (Figure 2), akinesia, catalepsy, ptosis and increased reactivity to painful stimuli and sounds.

Very marked anterograde degenerative changes were observed in the NA, DA and 5-HT nerve terminals of the telencephalon and diencephalon. Thus, practically no DA nerve terminals were observed in the nucleus caudatus-putamen, tuberculum olfactorium and nucleus accumbens. NA nerve terminals were found almost only in the preoptic area and the hypothalamus, although in markedly decreased numbers, whereas the NA nerve terminals of the neocortex, most limbic forebrain structures and the thalamus had more or less completely degenerated. Those portions of the preoptic area and the hypothalamus which still contained a considerable amount of NA nerve terminals were mainly the ventral part of the nucleus interstitialis striae terminalis, the lateral hypothalamic and preoptic area, the retrochiasmatic area, nucleus supraopticus, nucleus dorsomedialis hypothalami and nucleus periventricularis hypothalami. In some animals, however, practically all the NA nerve terminals had disappeared also in these regions. The DA nerve terminals of the median eminence were not affected by this lesion, however. The 5-HT nerve terminals of the nucleus suprachiasmaticus had completely disappeared. Since no nialamide treatment was performed, it is not possible to evaluate histochemically the degree of degeneration of the 5-HT nerve terminals in the other parts of the prosencephalon. The biochemically determined amine levels of the telencephalon of rats with the signs described above are shown in the Table. In some animals almost all the NA had disappeared in the same way as had occurred for 5-HT in many animals and for DA in practically all of the rats.

Markedly increased amine levels were observed in the NA, DA and 5-HT non-terminal axons ventral and lateral

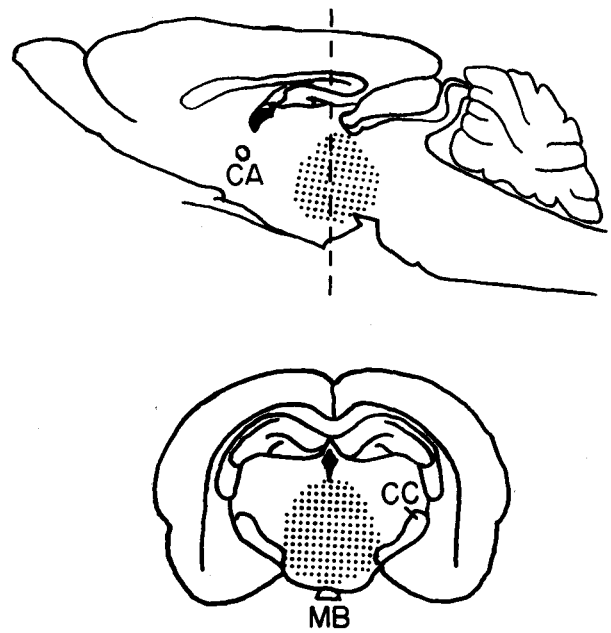

Fig. 1. Projection drawings showing a typical lesion producing effects such as hunched-back posture and catalepsy. CA = anterior commissure; MB = mammillary body; CC = crus cerebri.

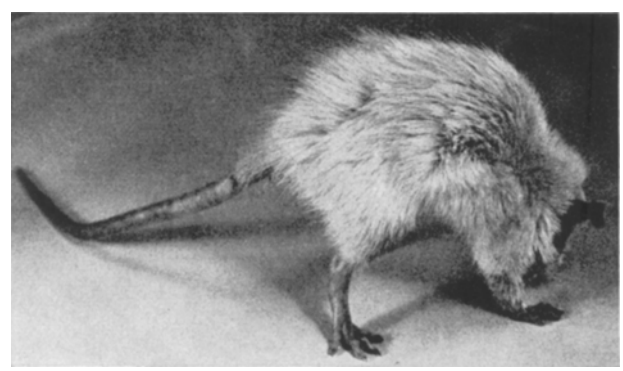

Fig. 2. Rat with a large mesencephalic-diencephalic lesion produced 14 days previously.

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to the lesion. The 5-HT fibres could be traced, however, only for a rather short distance from the lesion, whereas the NA fibres could be traced as far down as to the pons. The latter fibres were observed to form a dorsal and a ventral tegmental path in the mesencephalon. The DA nerve fibres from the DA cell bodies of the zona compacta of the substantia nigra ran ventral to the lemniscus medialis in a medioventral direction to ascend medial to the zona compacta among the oculomotor fibres. Retrograde cell body changes were observed in practically all catecholamine cell bodies in all the mesencephalic cell groups, in the cell bodies of locus coeruleus, of the tractus rubrospinalis in the pons, and of the reticular formation in the medulla oblongata and pons (A8–A10, A5–A7, A_1 according to [11]). During the first week there was a marked increase in the amine levels of many catecholamine cell bodies of the cell groups mentioned above. The cells also appeared swollen and showed more distinct processes than usual. After 4 weeks, however, the amine levels were no longer increased and in many mesencephalic cell bodies decreased amine levels were present. These nerve cells also appeared shrunk. During the first week after operation increased amine levels were observed also in many 5-HT cell bodies of nucleus raphe dorsalis and especially of nucleus raphe medianus (groups B7–B8 according to [11]). After 2–4 weeks there were observed also fairly marked increases in the number and intensity of the NA nerve terminals in the lower brain stem (e.g. the nucleus n. V and VII, the reticular formation of the pons and the medulla oblongata; see Figure 3) and in the cerebellum. In the few animals in which the spinal cord was studied, increases were usually observed also there in the number and intensity of the NA nerve terminals. The 5-HT terminals, however, showed no certain changes. Also biochemical assays revealed increases of NA in the pons plus the medulla oblongata and the cerebellum (Table) and sometimes also in the spinal cord. When the lesions were small or when the rats were in bad condition, these increases in intraneuronal NA were not observed.

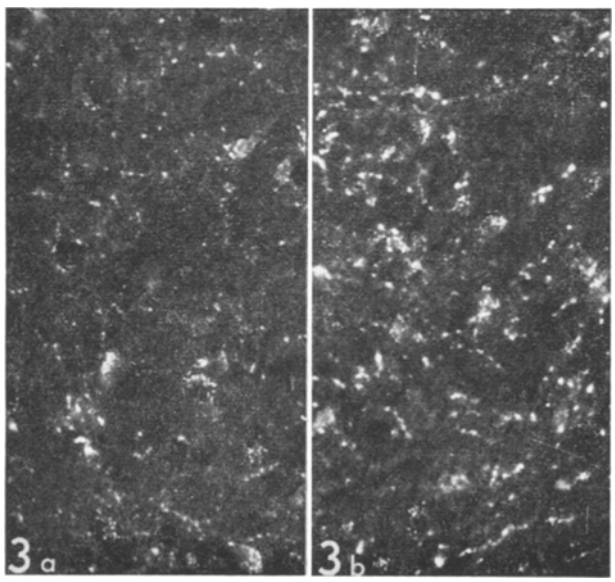

Fig. 3a. Nucleus cochlearis dorsalis of normal rat (cross section). A very low density of very fine noradrenalin nerve terminals is observed. × 280.

Fig. 3b. Nucleus cochlearis dorsalis of rat with a large mesencephalic-diencephalic lesion (cross section). Increased number of noradrenalin nerve terminals with increased fluorescence intensity are observed. × 280.

The results show definitely that the NA, DA and 5-HT nerve terminals of the telencephalon and diencephalon belong to large ascending neuron systems originating from the lower brain stem. One explanation for the simultaneous decrease and increase of the NA in the nerve terminals of the prosencephalon and the lower brain regions, respectively, may be that the NA storage granules produced in the cell bodies are accumulated in the transected non-terminal axons and transported in increased amounts down into the remaining axon branches of the NA neurons. This would mean that a single NA neuron has innervation areas situated far away from each other. It may thus innervate the telencephalon, the brain stem, and the cerebellum as well as the spinal cord.

The signs observed after the large lesions are in many respects similar to those found after reserpine treatment. Since in both cases there is a deficit of monoamines in the prosencephalon, it is tempting to assume that these effects are correlated. This has to be tested in future experiments[12].

Effect of large mesencephalic-diencephalic lesions on the levels (μg/g; mean $\pm$ s.e.m.) of 5-hydroxytryptamine (5-HT), dopamine (DA) and noradrenalin (NA) in different parts of the rat brain. In the lesion group only rats showing effects such as hunched-back posture are included

	Control group	Lesion group	Difference
5-HT in telencephalon	0.35 ± 0.019 (n = 14)	0.05 ± 0.010 (n = 25)	$P < 0.001$
DA in telencephalon	1.19 ± 0.067 (n = 14)	0.05 ± 0.014 (n = 25)	$P < 0.001$
NA in telencephalon	0.52 ± 0.034 (n = 14)	0.13 ± 0.011 (n = 25)	$P < 0.001$
NA in pons + medulla oblongata	0.65 ± 0.031 (n = 7)	1.02 ± 0.075 (n = 11)	$P < 0.01$
NA in cerebellum	0.18 ± 0.012 (n = 7)	0.26 ± 0.010 (n = 7)	$P < 0.01$

Zusammenfassung. Nach Ausführung von grossen symmetrischen mesencephalisch-diencephalischen Läsionen in Ratten konnte mit Hilfe von biochemischen und histochemischen Methoden eindeutig festgestellt werden, dass die Dopamin (DA), Noradrenalin (NA) und 5-Hydroxytryptamin (5-HT) enthaltenden Nerventerminalen im Prosencephalon zu grossen aufsteigenden DA, NA und 5-HT Neuronsystemen gehören. Die Zellkörper dieser Neuronensysteme sind im Gehirnstamm lokalisiert. Dies deutet darauf hin, dass ein einzelnes NA Neuron Gebiete innervieren kann, die weit auseinander liegen, zum Beispiel auf der einen Seite im Cerebellum, auf der anderen im Prosencephalon.

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[12] Acknowledgments: This study has been supported by grants (14X-502-02, 12X-714-02) from the Swedish State Medical Research Council, from 'Th. and J. Anderssons Minne' and from the Magnus Bergvall Foundation. For technical assistance we thank Miss B. Nilsdotter-Högberg, Mrs. M. Baidins, Miss B. Lindberg, and Mr. I. Olzon.