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CHANGES IN THE PITUITARY-TARGET GLAND SYSTEM FOLLOWING ELECTROLYTIC LESION OF MEDIAN EMINENCE AND HYPOPHYSEAL STALK IN MALE RATS

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There are numerous reports in the recent literature concerning dissociated atrophy, i.e. affecting only one of the target glands, in consequence of experimental lesion of the median eminence (gonads, Davidson and Ganong [4]; thyroid, Bogdanove and Halmi [3], Bogdanove [1], Bogdanove and D'Angelo [2]; adrenal, McCann and Haberland [8]). This dissociation of functional or structural changes in the target glands is often considered a specific effect of the localization of the foci of destruction. In the present paper some observations in connection with lesion of the median eminence and hypophyseal stalk will be reported.

Methods

The experiments were carried out in 82 young male Wistar rats of 100—200 g. body weight, kept on Larssen's diet and at uniform environmental temperature of 27° C. Lesions were placed by means of a Horsley—Clarke stereotaxic instrument. Hypophysectomy in a control series was performed with the usual parapharyngeal approach. — Animals with lesions in the median eminence were kept alive for 21—28 days postoperatively. At the end of the experiment animals were decapitated and the fresh weight of the hypophysis, adrenals, thyroids and gonads was measured with a torsion balance. One adrenal and the brain were fixed in 10 per cent formol, the other adrenal in Wiesel's fluid, thyroid and gonads were fixed in Heidenhain's susa mixture. In another group the brain was removed together with the pituitary and fixed in Bouin's fluid to study the extent of the stalk lesion in serial sections. Frozen sections of the adrenal fixed in formalin were stained with Sudan black. Other organs were embedded in celloidin-paraffin. Serial sections of the brain, gonads, thyroids and the other adrenal were stained with haematoxylin-eosin, the pituitary in alternating parallel series with Mann's methylblue-eosin, PAS and Gomori's aldehyde-fuchsin. Pituitaries fixed and embedded together with the hypothalamus were stained by the same methods.

Results

The material, according to localization of the lesion, can be divided into two main groups which shall be considered separately.

1. *Lesions of the anterior part* of the median eminence*

The weight of the endocrine glands in this group is indicated in the horizontal row *b)* of Table I. Characteristic of this group is a significant decrease

Table I

Body and organ weight after electrolytic lesion of median eminence and hypophyseal stalk

Group		No of rats	Body weight g.	Organ weights (mg.)			
				Hypophysis	Thyroid	Adrenal	Gonad
a) Control		15	165	7.1 ±0.2[1]	15.8 ±0.6	36.7 ±0.9	2276 ±46
b) Lesion of anterior part of median eminence		14	168	7.5 ±0.2	11.2[2] ±0.7	39.6 ±1.7	2128 ±64
c) Lesion of posterior part of median eminence and pituitary stalk	I	8	170	4.0[2] ±0.2	13.3 ±0.4	33.6 ±1.1	2175 ±52
	II	6	136	3.7[2] ±0.2 (3)[3]	14.4 ±1.2	33.8 ±3.1	1075[2] ±203
	III	6	179	4.0[2] ±0.3 (4)[3]	11.8[2] ±1.4	34.9 ±2.5	1265[2] ±219
	IV	17	158	3.5[2] ±0.2 (7)[3]	10,9[2] ±0.6	17.1[2] ±0.8	573[2] ±13

[1] Standard error.
[2] $p < 0.01$.
[3] Number of rats with measured pituitary weight (see Methods).

in thyroid weight and histological signs of inactivity in the thyroid (increase in colloid content, flattened follicular epithelium). Most typical of this group — especially when compared with the other to be described in paragraph 2 — is the normal hypophyseal weight and lack of any sign of atrophy of gonads and adrenals. The adrenals on the contrary were slightly increased in weight and displayed histologically a slight activation (narrow glomerular and sudanophobe zones, low lipoid content of the fascicular zone). Localization and extent of the lesion in this group is illustrated in Fig. 1. It has to be mentioned that in the large majority of these cases the most rostral part of the arcuate nucleus was affected by the lesion.

2. *Lesion of the posterior part of the median eminence or the pituitary stalk*

Weight changes of the pituitary and the target glands are shown in Table I, in the lower rows (c). Characteristic of this experimental group is a

* Meaning the region anterior from a frontal plane passing through the point where on the basal surface of the brain the beginning of the stalk can be recognized.

significant (40—50 per cent) decrease in pituitary weight with or without atrophy of the target organs. According to the number of endocrine organs affected the material can easily be divided into four groups as follows.

I. group. Decreased pituitary weight, peripheral endocrine organs intact.

II. group. Decreased pituitary weight, gonads atrophic, thyroid and adrenals intact.

III. group. Decreased pituitary weight, atrophic gonads and thyroid, adrenals intact.

IV. group. Decreased pituitary weight, severe atrophy of the gonads, thyroid and the adrenals.

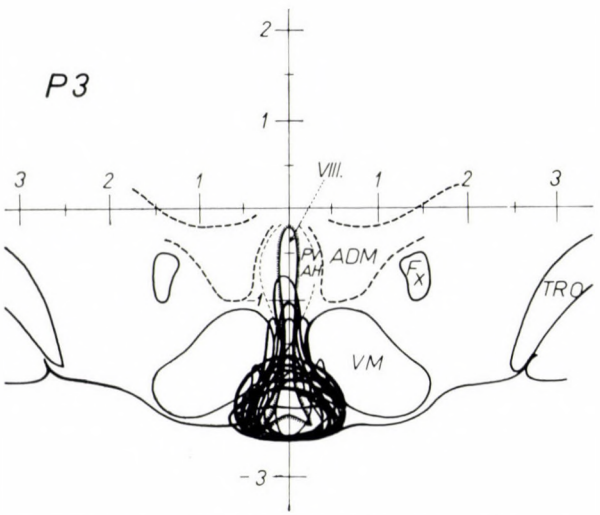


Fig. 1. Outlines of 14 focal hypothalamic lesions placed into the anterior part of median eminence. Albino rat, frontal plane P 3 (with reference to bregma). Horizontal zero plane 8 mm. below bregma. Scale in mm. ADM = dorsomedial area, Fx = columna fornicis, PVAH = anterior periventricular nucleus, TRO = optic tract, VM = ventromedial nucleus, V. III. = third ventricle

The degree of lesion of the posterior median eminence or the pituitary stalk, as revealed by the histological study of serial sections, corresponds fairly exactly with this grouping of the consequences on the endocrine glands. Atrophy affecting the hypophysis as well as the three target glands (group IV) is observed exclusively when the posterior part of the median eminence or the pituitary stalk is totally or almost totally destroyed/interrupted. In the other groups, too, the degree of the lesion runs clearly parallel with the number of the endocrine glands affected, the lesion being smallest in group I and consequently larger in groups II and III. — Perhaps the most remarkable observation in this series — demonstrated in Table II — is that there was not a single case in the whole series with thyroid atrophy without gonadal atrophy

and no adrenal atrophy without clear gonadal and thyroid atrophy. This clearly indicates that in posterior median eminence or pituitary stalk lesion the male gonad is the most sensitive gland after the pituitary, the thyroid being less, and the adrenal least, susceptible to atrophy.

Table II

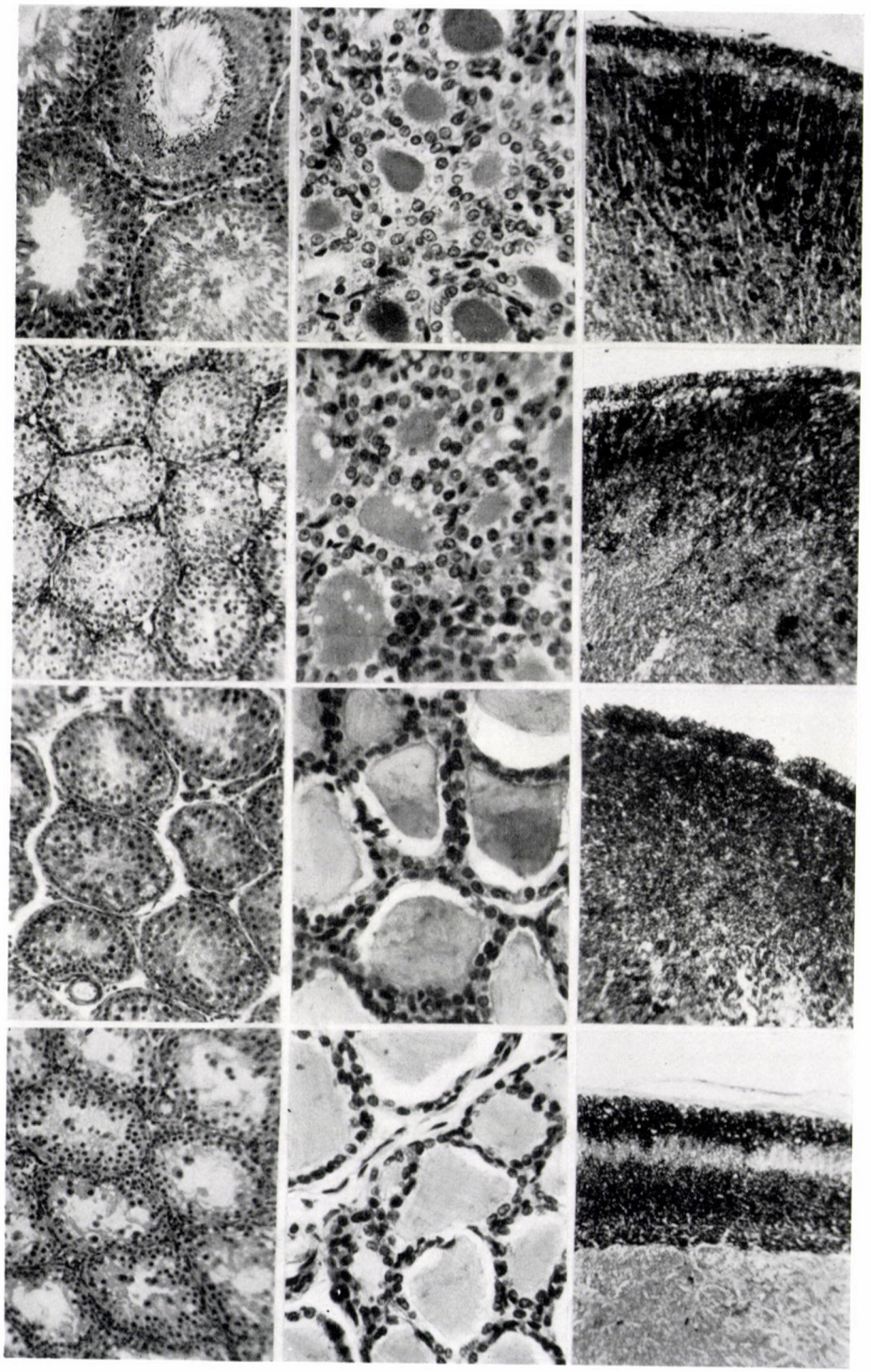
Distribution of atrophy in different endocrine glands after electrolytic lesions of posterior median eminence and hypophyseal stalk

Group	Atrophy of				No of rats
	Pituitary	Gonad	Thyroid	Adrenal	
I	+	0	0	0	8
II	+	+	0	0	6
III	+	+	+	0	6
IV	+	+	+	+	17
No of cases	37	29	23	17	37

The degree of histological atrophy of the pituitary runs of course fairly parallel with the extension of the lesion of the posterior median eminence or the stalk. After total or almost total destruction of the posterior median eminence or interruption of the stalk, the anterior lobe as known from many descriptions in the literature is completely degranulated, with extensive fibrosis of the central parts, and devoid of basophil or PAS positive cells. After partial (*e.g.* unilateral) destruction of the posterior median eminence or interruption of the stalk the atrophy is also partial, the regions of the anterior lobe corresponding (sagittally) with the lesion being completely atrophied, while those corresponding to the intact parts may seem almost normal histologically. It were of course difficult to establish even from the complete section series how extensive a part of the anterior lobe is needed to maintain the gland's normal function.

Fig. 2 demonstrates the histological state of one representative case in each group. The degree of destruction varies of course considerably even within one group, especially in the gonad. In light cases only spermiohistogene-

Fig. 2. Histological appearance of the target organs (testis, thyroid and adrenal) after posterior median eminence or pituitary stalk lesion, representative for grouping (I—IV). First horizontal row: Group I, no histological change in either organ. Second row: Group II, testicular atrophy, unchanged thyroid and adrenal. Third row: Group III, testicular atrophy, inactive thyroid, unchanged adrenal. Bottom row: Group IV, testicular atrophy, inactive thyroid, atrophic adrenal (Magnification: 90×, 320×, 90×)



sis seems to be affected. Nevertheless, in groups II and III some severely atrophied, almost post-hypophysectomy like testes were also encountered. In group IV all gonads were completely atrophic. — Atrophy of the thyroids was always associated with histological signs of inactivity (large follicles and flattened epithelium). — The atrophy of the adrenals besides a decrease in weight, was characterized by a relatively broad glomerular zone rich in lipoids, a broad sudanophobe and narrow fasciculate and reticular zones. In some cases which had to be listed with groups II and III, the adrenal was slightly hypertrophic.

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Taking into consideration the report of McCann and Haberland [8] who observed isolated adrenal atrophy after lesioning the median eminence, it seemed to be necessary to investigate the time course of events taking place after the lesion. It were conceivable that the atrophy of one target organ may develop sooner than that of the other, thus giving a distorted picture. Unfortunately, the duration of postoperative survival has not been indicated in McCann and Haberland's report. Since with electrolytic lesions there is always an element of uncertainty, it seemed more reliable to investigate the question after hypophysectomy. The results of this control series are shown in Table III. It appears that the adrenal 7 days after hypophysectomy had lost 40 per cent of its weight, while weight and histological structure of the gonads was still normal. Serious gonadal atrophy was seen only on the 10th day.

Table III

Weight of target organs at different intervals after hypophysectomy

Days after hypophysectomy	No of rats	Body weight g.	Organ weights (mg.)		
			Adrenal	Thyroid	Gonad
Control	4	105	23.4 ± 1.4[1]	10.5 ± 0.8	1650 ± 50
3	3	120	23.5 ± 1.2	13.0 ± 0.6	1670 ± 41
7	3	116	14.0[2] ± 1.8	10.8 ± 0.2	1620 ± 42
10	3	111	13.8[2] ± 0.5	10.2 ± 0.7	800[2] ± 25
15	3	100	8.0[2] ± 0.6	8.7[2] ± 0.5	530[2] ± 61

[1] Standard error.
[2] $p < 0.01$.

Discussion

It emerges clearly from the present experiments that it is the weight of the hypophysis that reacts most sensitively to destruction of the posterior median eminence or interruption of the stalk. The weight loss as well as the histological findings show that it cannot be the atrophy of the neural lobe which accounts for the decrease in total weight. In addition, the weight loss of the posterior lobe is probably over-compensated by the hypertrophy of the intermediate lobe occurring under such circumstances (HÁMORI [7]). It seems therefore highly advisable carefully to determine the weight of the pituitary in all experiments with hypothalamic lesions. — From the target organs the male gonad appears to be the most, the thyroid less and the adrenal least sensitive to posterior median eminence or stalk lesion.

The same susceptibility of the target organs to partial pituitary resection has been observed by SMITH [10] in the rat, and by GANONG and HUME [6] in the dog. On removing progressively larger parts of the anterior lobe, first gonadal atrophy appeared, later that of the thyroid, and only after ablation of the largest part could adrenal atrophy be observed. No other sequence has ever been observed to occur under such circumstances. — Complete accordance between these two types of experiments have indicated that focal destruction of the posterior part of the median eminence as well as partial destruction of the stalk induce a panhypopituitarism which according to its intensity may cause gonadal atrophy only or gonadal and thyroid atrophy, or in the most severe cases gonadal, thyroid and adrenal atrophy. From this point of view, "isolated" gonadal atrophy often observed after hypothalamic lesions must by no means be the result of the destruction of nervous structures specific for the maintenance of gonadotrophic functions. This is especially true for the gonadal atrophy usually occurring after posterior tuberal lesions (*e.g.* DAVIDSON and GANONG [4]); this atrophy is the effect of moderate panhypopituitarism rather than of the lesion of some specific gonadotrophic control mechanism.

According to our control series, the isolated adrenal atrophy described by MCCANN and HABERLAND [8], is easily explained by the different time course of the atrophy of target organs. 6—8 days after hypophysectomy when the adrenal has already undergone considerable atrophy the gonad may be quite intact. The progress of atrophy may even be slower in case of median eminence lesion. This assumption is supported by some of our observations not dealt with in the present paper, namely that 9 days after total coagulation of the stalk the animals displayed considerable adrenal atrophy with intact gonads. According to these findings we could accept the occurrence of isolated hypothalamic adrenal atrophy only if it could be observed in cases with intact gonads and thyroids at least 2 weeks postoperatively. The slight adrenal hyper-

trophy observed after median eminence or stalk lesion (similar observations have been made earlier by McCann and Sydnor [9] and in this institute by Fülöp [5]) cannot explained for the time being.

Isolated thyroid atrophy after hypothalamic lesion can be accepted as a genuine specific effect if it is seen in animals with intact gonads and without weight reduction of the pituitary. The observations after anterior median eminence lesions completely satisfy these criteria, so that the findings of Bogdanove and Halmi [3], Bogdanove [1], Bogdanove and D'Angelo [2] and their explanation must be accepted. — On the other hand, atrophy of the thyroid occurring after posterior median eminence or stalk lesion must be considered only as a part effect of the panhypopituitarism.

Summary

Changes in weight and histology of the anterior pituitary gland and the target organs occurring after experimental lesion of the median eminence and the hypophyseal stalk have been studied. After lesion in the anterior part of the median eminence thyroid atrophy develops which is considered to be of neurogenic nature. — After lesions of the posterior median eminence or the hypophyseal stalk the pituitary is always reduced in weight and depending from the degree of the lesion a gonadal, or gonadal and thyroid, or in the most severe cases, gonadal, thyroid, and adrenal, atrophy develops. Three weeks after posterior median eminence or stalk lesion no isolated thyroid or adrenal atrophy has been observed. — The isolated adrenal atrophy occasionally observed after median eminence lesion is explained on the basis of the time course of the atrophy, which develops much quicker in the adrenal than, especially, in the male gonad. — Since to posterior median eminence lesion as well as progressive subtotal hypophysectomy the male gonad is most susceptible, somewhat less the thyroid and least the adrenal, endocrine atrophy occurring after lesions in the posterior median eminence is considered to result from panhypopituitarism which according to the size and localization of the lesion may vary in degree and therefore affect the gonad alone, or the gonad and the thyroid together, and only in the most severe cases affect all of the target organs.

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VERÄNDERUNGEN DER HYPOPHYSE UND DER PERIPHEREN ENDOKRINEN DRÜSEN NACH ELEKTROLYTISCHER LÄSION DER EMINENTIA MEDIANA UND DES HYPOPHYSENSTIELS AN MÄNNLICHEN RATTEN

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Nach experimenteller Läsion der Eminentia mediana und des Hypophysenstiels wurde das Gewicht des Hypophysenvorderlappens und der peripheren endokrinen Drüsen sowie in ihrer histologischen Struktur eintretenden Veränderungen untersucht. Nach der Läsion des vorderen Gebietes der Eminentia mediana entwickelte sich eine Schilddrüsenatrophie, die einen spezifischen neuralen Effekt darstellen dürfte. Bei Zerstörungsherden des hinteren Gebietes der Eminentia mediana und des Hypophysenstiels verminderte sich das Gewicht der Hypophyse in jedem Fall, ferner entwickelte sich je nach dem Grad der Läsion Gonaden-, Gonaden- und Schilddrüsen- bzw. Gonaden-, Schilddrüsen und Nebennierenatrophie. Drei Wochen nach Läsionen des hinteren Gebietes der Eminentia mediana und des Hypophysenstiels konnte niemals eine isolierte Schilddrüsen- oder Nebennierenatrophie nachgewiesen werden. — Eine isolierte Nebennierenatrophie — die nach Läsion der Eminentia mediana von anderen Autoren beschrieben wurde — wird mit zeitlichen Ablauf der Atrophisierung erklärt. Die Nebennierenatrophie entwickelt sich nämlich viel rascher als die Atrophie der männlichen Gonaden. Da auf eine Läsion des hinteren Gebietes der Eminentia mediana sowohl, als auch auf eine progressive partielle Hypophysektomie die Gonaden am empfindlichsten, die Schilddrüse etwas weniger empfindlich und die Nebennieren am wenigsten empfindlich reagieren, wird die nach Läsion des hinteren Gebietes der Eminentia mediana entstehende Atrophie der innersekretorischen Organe als Folge eines Panhypopituitarismus betrachtet der je nach Ausmaß und Lokalisation der Schädigung verschieden schwer sein kann, und entweder nur die Gonaden, oder die Gonaden und die Schilddrüse jedoch nur in den schwersten Fällen alle drei peripheren endokrinen Drüsen erfaßt.

ИЗМЕНЕНИЕ СИСТЕМЫ «ГИПОФИЗ—ПЕРИФЕРИЧЕСКИЕ ЭНДОКРИННЫЕ ЖЕЛЕЗЫ» ПОСЛЕ ЭЛЕКТРОЛИТИЧЕСКОГО ПОВРЕЖДЕНИЯ EMINENTIA MEDIANA И НОЖКИ ГИПОФИЗА У КРЫС-САМЦОВ

Б. ХАЛАС, Л. ПУПП и Ш. УХЛАРИК

Авторы, после экспериментально вызванного повреждения **eminentia mediana** и ножки гипофиза, исследовали изменения, наблюдаемые в весе и гистологической структуре передней доли гипофиза и периферических эндокринных желез. При повреждении передней области **eminentia mediana** развивалась атрофия щитовидной железы; авторы рассматривают это как специфический невральный эффект. После повреждения задней области **eminentia mediana** и ножки гипофиза, вес гипофиза во всех случаях снижался и, в зависимости от степени повреждения, развивалась атрофия половых желез или половых желез и щитовидной железы, или половых желез, щитовидной железы и надпочечников. Через три недели после повреждения задней области **eminentia mediana** и ножки гипофиза, не удавалось выявить изолированную атрофию щитовидной железы или надпочечников. — Изолированную атрофию надпочечников — описанную другими авторами после повреждения **eminentia mediana** — авторы данной статьи объясняют различной хронологией развития атрофий. Он выявили, что атрофия надпочечников развивается раньше, чем атрофия мужских половых желез. Ввиду того, что на повреждение задней области **eminentia mediana** как и на прогрессивную частичную гипофизэктомию наиболее чувствительно реагируют половые железы, несколько менее чувствительно — щитовидная железа, а меньше всего реагируют надпочечники, то авторы рассматривают атрофию эндокринных желез, возникающую после повреждения задней области **eminentia mediana** — как пангипопитуитаризм, который, в зависимости от распространения и локализации повреждения, может быть различной степени и может распространяться либо только на половые железы, либо вместе на половые железы и щитовидную железу, и только в самых тяжелых случаях охватывает все три периферические эндокринные железы.

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