activities of desamino[1]-arginine-vasopressin, only that on the chicken blood pressure is higher than the corresponding potency of arginine-vasopressin. The suppression of the N-terminal amino group of arginine-vasopressin does not equally affect the so-called vasopressin-like activities. The pressor activity is practically unchanged, whereas the antidiuretic potency is approximately tripled. With an antidiuretic activity of 1300 IU/mg, desamino-arginine-vasopressin is the most active compound so far found in the field of the neurohypophysial peptides. The dose-response curves of arginine-vasopressin (International Standard) and desamino[1]-arginine-vasopressin shown in the Figure were obtained in 6 rats by repeating each dose ten times in a fully randomized sequence. Statistical analysis showed that the calculated dose-response curves can be regarded as parallel. Consequently the high antidiuretic activity of desamino[1]-arginine-vasopressin is not confined to a particular dose range, but can be considered as generally valid.

Zusammenfassung. Die Synthese und die pharmakologischen Haupteigenschaften von Desamino[1]-Arginin-Vasopressin werden beschrieben. Dieses Peptid ist durch eine hohe (1300 IE/mg) und relativ selektive antidiuretische Wirksamkeit ausgezeichnet.

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Gonadotrophic Activity in Hypothalamic Extracts

It has been published repeatedly that some hypothalamic extracts can release the pituitary hormones. Several authors claimed success in obtaining a hypothalamic extract with LH releasing activity[1-4]. The depletion of ovarian ascorbic acid, the direct visualization of the tubal ova, the appearance of recent corpora lutea in the androgenized sterile female rat, were used as a test of the LH release. The extracts used by these authors were prepared from rat or sheep brains.

Guillemin[4] reported that the administration of hypothalamic extracts to sterile rats produced corpora lutea, and concluded from this and other evidence that these extracts contained an LH releasing factor. For the general work of our laboratory, it was important to check this conclusion in the androgenized sterile hypophysectomized rats.

Sheep hypothalamic extracts were prepared, following exactly the indication given by Guillemin. Sterile rats were obtained by means of injecting them with 200 μg of testosterone propionate on the 4th day after birth.

Animals were used when adult; some of them were hypophysectomized by way of parapharingeal or transauricular technique. Extracts were injected intravenously immediately after they were prepared. When hypophysectomized sterile rats were used, extracts were injected after the operation, as soon as the animal had recovered. Injected animals were killed 48–72 h after the injection. Immediately before the injection of the extract one of the ovaries was removed, weighed, fixed in Helly solution and kept as control of the action of the extracts. Weight and appearance of the corpora lutea were taken as indicators of gonadotrophic activity.

In the first experiment 6 sterile rats and 8 hypophysectomized sterile rats were injected with hypothalamic extracts. Corpora lutea were found in the ovaries of all the sterile rats and five out of eight hypophysectomized sterile rats showed also corpora lutea after the injection of hypothalamic extracts. In all the injected animals the weight of the remaining ovary increased. This experiment showed clearly that the production of corpora lutea cannot be attributed to an LH releasing factor but to an intrinsic gonadotrophic activity of the hypothalamic extracts (Figure 1).

A second experiment was undertaken in order to verify whether the gonadotrophic activity was found throughout the whole hypothalamus or concentrated in the region of the median eminence.

Eight sterile female rats were injected with extracts prepared from the region of the median eminence (Figure 2) and eight other rats with extracts prepared with the remaining hypothalamus.

Every animal of the group injected with the extracts from the median eminence showed corpora lutea in their ovaries, whereas the presence of corpora lutea among the animals of the group injected with the 'remaining' hypothalamus was shown by only one of them. This experiment pointed out that the gonadotrophic activity of the hypothalamic extracts was higher in the region of the median eminence than in the remaining hypothalamus. It is convenient to remember that the neurohypophyseal tissue which constitutes the median eminence and the

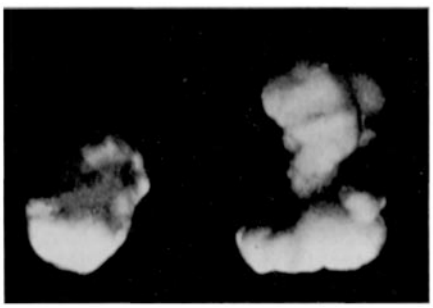

Fig. 1. Ovaries of a sterile hypophysectomized rat. Left: the ovary removed before injection of the extract. Right: the remaining ovary 48 h after injection of hypothalamic extract.

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pituitary stalk lies side by side with the pars tuberalis of the adenohypophysis (Figure 2). When an extract of the median eminence region is prepared, the material contains not only neurohypophyseal tissue but pars tuberalis also.

For proper evaluation of the results obtained with hypophysectomized animals, it is important to keep in mind that the gonads of hypophysectomized animals react in a different way from those of normal animals[1,5,6]. All these facts should be taken into account when the gonadotrophic releasing activity of a hypothalamic extract is claimed to have been found. Enough evidence has been accumulated to admit the existence of a central nervous system control of the pituitary gland, but doubts may be cast on some of the experiments which claimed success in obtaining hypothalamic extracts with gonadotrophic releasing activity. Our experiments show that GUILLEMIN's extracts have intrinsic gonadotrophic activity.

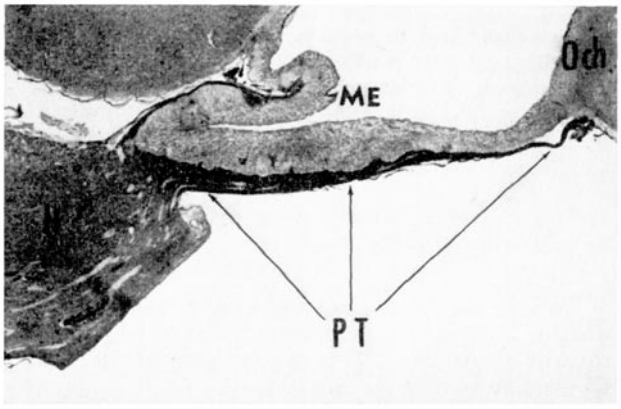

Fig. 2. Sagittal section of the hypothalamic region of sheep. H: hypophysis. O.ch.: optic chiasm. M.E.: median eminence. P.T.: pars tuberalis.

Résumé. Si l'on administre à des rats stériles par testostérone des extraits hypothalamiques de mouton préparés suivant la technique de GUILLEMIN, on déclenche l'apparition des corps jaunes aussi bien chez les rats entiers que chez les animaux privés d'hypophyse. Ces extraits ont une activité gonadotrophique intrinsèque.

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D-Aminosäurehaltige Analoga des Eledoisins[1,2]

Bei der Mehrzahl der durch Aminosäureaustausch synthetisierten Peptidwirkstoffanaloga wurde als austauschende Aminosäure eine strukturell verwandte Aminosäure, eine Aminosäure mit gleicher oder entgegengesetzter Polarität oder eine Aminosäure, die durch das Einführen, Weglassen oder durch Substitution einer funktionellen Gruppe entstanden ist, verwendet. Ein anderer Weg wurde vor einiger Zeit in unserem Laboratorium zur Beurteilung der Bedeutung jeder einzelnen individuellen Aminosäure für die biologische Aktivität eingeschlagen und systematisch jede Aminosäure des Bradykinins gegen Alanin ausgetauscht und so die Reihe Ala^1- bis Ala^9-Bradykinin synthetisiert[3].

In ähnlicher Weise haben wir in dem C-terminalen, die Aminosäuren 5–11 umfassenden Heptapeptidanalogon des Eledoisins:

5 6 7 8 9 10 11
H-Gly-L-Ala-L-Phe-L-Val-Gly-L-Leu-L-Met-NH_2,

das anstelle der Asparaginsäure in Position 5 einen Glycylrest und anstelle des Isoleucins in Position 8 einen Valylrest enthält und das auf molarer Basis etwa 30% der Aktivität des Eledoisins besitzt[4], alle optisch aktiven Aminosäuren jeweils gegen die entsprechende D-Aminosäure ausgetauscht. Darüber hinaus wurden weitere Analoga mit 2, 3 und 4 D-Aminosäuren sowie die All-D-Verbindung mit 5 D-Aminosäuren synthetisiert. Ferner wurden zwei Heptapeptide mit je einer D-Aminosäure zu den eledoisinanalogen Undekapeptiden verlängert.

In der Tabelle sind für diese Verbindungen die Grenzdosen für die Kontraktion des Meerschweinchen-Ileums und für die Senkung des Kaninchenblutdruckes zusammengestellt und die relativen Aktivitäten bezogen auf das All-L-Heptapeptidanalogon = 100 angegeben. Zur Ermittlung dieser Relationen wurden die Dosis-Wirkungskurven in der graphischen Darstellung % Senkung = f (log Dosis) herangezogen.

Wird eine der C-terminalen 5 Aminosäuren gegen die entsprechende D-Aminosäure ausgetauscht, so führt das zu einer Reduktion der Aktivität auf unter 1%. Die

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