THE EFFECT OF THE METHOD OF ADMINISTRATION ON THE MORPHOGENETIC ACTIONS OF PROGESTERONE

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It has recently been shown that if progesterone is administered intraperitoneally in sufficiently high doses it causes deep anaesthesia, while subcutaneous administration of the same or even of still higher doses exerts no such effect. This has been attributed to the greater rapidity with which it is absorbed from the peritoneum than from the subcutaneous tissue. The fact that the rate of absorption plays a particularly important role in determining the anaesthetic potency of progesterone is well shown furthermore by the observation that intravenous administration of this compound in propylene glycol causes almost immediate anaesthesia (Selye, 1941a).

It appeared of interest in this connexion to establish whether there is any noticeable difference between the morphogenetic actions of intraperitoneally and intravenously administered progesterone. Since some of the actions of this hormone are also significantly influenced by the pituitary (Selye, 1940; Selye & Bassett, 1940) it was deemed of value to reinvestigate, in connexion with the above-mentioned problem, the difference in the response of the intact and hypophysectomized progesterone-treated animal.

EXPERIMENTAL

Forty female albino rats, having an average weight of 62 g. (range 56–71 g.), were divided into the following five groups of eight rats each: (1) untreated, (2) subcutaneously injected with progesterone, (3) intraperitoneally injected with progesterone, (4) hypophysectomized and subcutaneously injected with progesterone, (5) not injected, hypophysectomized. The rats were treated every 2 days, first with a dose of 3 mg./day, and this amount was gradually increased up to 10 mg./day. This gradual increase in the amount of progesterone given was essential because the animals receiving the hormone intraperitoneally were definitely anaesthetized after each injection during the first few days and, as previous experiments have shown, the daily dose must be raised gradually in order to obtain adaptation to the narcotic effect of this compound (Selye, 1941b). The progesterone was dissolved in peanut oil in a concentration of 40 mg./ml. Since it has been shown by Selye & Bassett (1940) that progesterone exerts a marked diuretic action both in the intact and even more so in the hypophysectomized rat, it was also decided to follow the urine output of the experimental animals. In order to make this possible with a reasonable degree
of accuracy, each rat was placed in a special metabolism cage of a type designed in this laboratory to make possible complete separation of food, faeces and urine (Selye et al. 1941). The urine volume was measured daily.

The results of this experiment are summarized in Table 1 and Fig. 1, in which the average organ weights and urine volume are registered as well as the percentage deviation of these values from those of the intact controls. It is readily seen that subcutaneous injection of progesterone causes marked adrenal atrophy in the intact rat, which confirms previous observations (Selye & McKeown, 1935). On the other hand, if the same amount of the hormone is administered intraperitoneally it causes no significant change in adrenal weight; indeed, the adrenals in this group are slightly larger than those of untreated controls. In the hypophysectomized animal progesterone failed to influence adrenal weight. The ovarian and thymus atrophy which is usually caused by subcutaneous progesterone administration was well marked in this series and, although even intraperitoneal administration of the hormone elicited a slight decrease in the average weight of these organs, the atrophy was by no means as pronounced as after subcutaneous injection. Conversely, the uterus, which increases in size under the influence of progesterone, shows a more pronounced hypertrophy following subcutaneous than following intraperitoneal injections. This uterine hypertrophy elicited by progesterone in animals not pretreated with oestrin was first described by Selye (1940), who demonstrated, furthermore, that it may also occur in the absence of the pituitary. The present experimental series shows that owing to the marked atrophy of the uterus which develops following ablation of the pituitary the metrotropic effect of the hormone is even more pronounced in the hypophysectomized than in the intact animal. It is of special interest in this connexion that, although the ovaries and adrenals of the hypophysectomized animal are not modified by progesterone treatment, the thymus-weight-decreasing effect

Table 1. Effect of progesterone on the weight of various organs and diuresis in the intact and hypophysectomized rat

|                      | Controls | Progesterone s.c.* | Progesterone i.p.* | Hypophys- | Hypophys- |
|----------------------|----------|--------------------|--------------------| ectomized| ectomized|
| Body weight in g.    | 77·0     | 80·0               | 83·0               | 63·0     | 58·0     |
| Adrenal weight       | 22·1     | 16·3               | 23·7               | 6·0      | 5·8      |
| Thymus weight mg.    | 173·0    | 110·0              | 150·0              | 48·3     | 122·0    |
| Ovary weight mg.     | 14·6     | 5·8                | 7·3                | 4·15     | 3·5      |
| Uterus weight mg.    | 55·0     | 203·0              | 145·0              | 167·0    | 19·9     |
| Urine volume ml.     | 3·8      | 4·5                | 5·2                | 8·7      | 4·1      |
| Average/day during   |          |                    |                    |          |          |
| experiment           |          |                    |                    |          |          |
| Percentage deviation | 0        | +18·0              | +37·0              | +129·0   | +7·0     |

* s.c. = subcutaneous. i.p. = intraperitoneal.
Fig. 1. Effect of subcutaneous and intraperitoneal progesterone administration on the weights of various organs. In this curve the average organ weights are given in a manner to indicate the percentage deviation from the untreated control values which are taken to be 100. Since the uterine weights are very high in proportion to those of other organs, the scale is changed above the base level of 100 for the columns representing the uterus.
of the hormone is likewise more pronounced in the absence than in the presence of the pituitary.

The diuretic action of progesterone was only insignificantly greater in the intact rats receiving the hormone intraperitoneally than in those receiving it by subcutaneous injection. In this respect the method of administration does not appear to be of great importance. On the other hand, it is quite evident from the figures given in Table 1, which represent the average daily output over the entire experimental series, that the diuretic effect of progesterone is very much more pronounced in the absence than in the presence of the hypophysis. This is in agreement with the assumption of Selye & Bassett (1940), who believe that some pituitary factor counteracts the diuretic action of progesterone in the intact animal.

Histological examination of the mammary glands showed no significant development of the acinar system in any of the groups except that of the intact animals receiving progesterone by the subcutaneous route. The fact that in the hypophysectomized animals the same dose of this hormone administered in the same manner failed to cause significant mammary gland development is not surprising, since previous experiments have shown the important role played by the hypophysis in the mammotrophic action of this steroid. It is noteworthy, however, in connexion with the main problem discussed in this paper, that intraperitoneal administration proved almost entirely ineffective even in the presence of the hypophysis.

In order to obtain further evidence corroborating the data described above we performed a second experiment under practically the same conditions as the first. Since the results were in every respect very similar to those of the first series, we shall omit a detailed description of the relevant data here. It is sufficient to mention that the only significant deviation from the first experiment was that the urine volume was slightly higher in the intact rats receiving progesterone subcutaneously than in those obtaining the hormone intraperitoneally. The data of both these experiments indicate that in this respect the method of administration is of no great importance.

**SUMMARY**

Experiments on the rat indicate that although intraperitoneal administration of progesterone—which leads to rapid absorption of the hormone—is more effective in producing anaesthesia than subcutaneous injection, the reverse is true of the morphogenetic actions of progesterone. Thus subcutaneous injection of this hormone is more effective than intraperitoneal administration with regard to its ability to cause atrophy of the adrenal cortex, thymus and ovaries or hypertrophy of the uterus.

The diuretic action of progesterone is apparently independent of the method of administration under the conditions of the present experimental series.

It is noteworthy that in the absence of the hypophysis the thymus atrophy,
uterine hypertrophy, and diuresis caused by progesterone are much more pronounced than in the presence of this gland.

Histological examination showed, furthermore, that the mammotrophic effect of progesterone is much more pronounced in the case of subcutaneous administration than it is after intraperitoneal injection. Thus of all the progesterone effects so far examined, only the anaesthetic action proved to be more evident following intraperitoneal administration of the compound than following its injection into tissues from which it is presumably more slowly absorbed.

These experiments furnish additional evidence emphasizing the importance of the method of administration for the action of hormones.

The expenses of this investigation were defrayed through a grant received from the Blanche E. Hutchinson Fund of McGill University. The progesterone was kindly donated by Dr Gregory Stragnell and Dr Erwin Schwenk of the Schering Corporation, Bloomfield, New Jersey.

REFERENCES