EFFECT OF 5-METHOXYTRYPTOPHOL ON THE REPRODUCTIVE SYSTEM OF MALE RATS

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It is a well-known fact that the pineal gland contains a large amount of indole substances chemically related to serotonin (Axelrod, 1970). Among these compounds, melatonin has been the most extensively studied (Reiter & Sorrentino, 1970). Many reports have described that melatonin displays an evident inhibitory influence on the sexual functions when administered parenterally or by implant into the hypothalamus (Chu, Wurtman & Axelrod, 1964; Fraschini, Mess & Martini, 1968; Debeljuk, 1969; Debeljuk, Feder & Paulucci, 1970a). Another indole, 5-methoxytryptophol, isolated from the pineal gland by McIsaacs, Taborsky & Farrell (1964), was also shown to have inhibitory effects on the sexual system, although some of its properties seem to be somewhat different from those of melatonin (Fraschini, 1969). Since the effect of the treatment with 5-methoxytryptophol has been only partially investigated in male rats, it has been considered of interest to study the effect of the parenteral administration of this indole on the reproductive system of prepubertal and pubertal male rats.

Male rats of the Wistar strain were maintained under constant environmental conditions (14 hr light/10 hr dark) and allowed unrestricted access to standard laboratory chow and water. In the first part of the experiment, 21-day-old male rats were injected subcutaneously (s.c.) with 100 or 300 µg of 5-methoxytryptophol/rat/day over a period of 21 days. The 5-methoxytryptophol (Sigma Chemical Company) was dissolved in absolute ethanol, diluted to 10% before injection, and administered in a volume of 0.5 ml/rat. Control rats under similar environmental and feeding conditions were injected daily with 0.5 ml 10% ethanol in saline/rat. In the second part of the experiment, 30-day-old male rats were used. They were also injected with 100 or 300 µg 5-methoxytryptophol dissolved in the same way as described above. Control rats were injected with 0.5 ml 10% ethanol solution. At the end of the 21-day treatment period, the animals from both experiments were decapitated, and the weights of the anterior pituitaries, testes, seminal vesicles, and ventral prostates, were recorded. The significance of the differences in organ weights between control and experimental groups was tested by means of Student's *t* test in the first part of the experiment, and by means of the variance analysis in the second part.

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From the results presented in Table 1, it is evident that daily doses of 100 μg 5-methoxytryptophol resulted in a slightly reduced growth of all the reproductive organs studied when the treatment started at 21 days of age. In no case, however, were the differences statistically significant. On the other hand, treatment with daily doses of 300 μg 5-methoxytryptophol was effective in significantly decreasing ($P < 0.001$) the weight of the ventral prostates (Table 2). The weight of the testes, anterior pituitaries, and seminal vesicles, although lower in the 5-methoxytryptophol-treated group when compared with those of the controls, did not show statistically significant differences. In the second part of the experi-

TABLE 1
EFFECTS OF THE TREATMENT WITH 5-METHOXYTRYPTOPHOL ON SEXUAL STRUCTURES OF MALE RATS

Treatment*	Final body weight (g)	Anterior pituitary weight (mg)	Testes weight (mg)	Seminal vesicle weight (mg)	Ventral prostate weight (mg)
Control (12)	101.91 ± 2.27	3.47 ± 0.13	1028.33 ± 2.27	32.75 ± 2.82	37.75 ± 5.07
5-Methoxytryptophol (16)	96.31 ± 2.86	3.23 ± 0.15	900.75 ± 48.36	27.81 ± 2.73	26.92 ± 2.50

Rats received s.c. injections of 5-methoxytryptophol (100 $\mu\text{g}/\text{day}/\text{rat}$) from 21 days of age for a period of 21 days. Values are means $\pm$ S.E.

* Number of animals in parentheses.

TABLE 2
EFFECTS OF THE TREATMENT WITH 5-METHOXYTRYPTOPHOL ON SEXUAL STRUCTURES OF MALE RATS

Treatment†	Final body weight (g)	Anterior pituitary weight (mg)	Testes weight (mg)	Seminal vesicle weight (mg)	Ventral prostate weight (mg)
Control (19)	97.89 ± 4.15	3.20 ± 0.17	1048.63 ± 41.98	39.68 ± 3.30	32.36 ± 2.63
5-Methoxytryptophol (20)	96.85 ± 4.97	2.87 ± 0.23	956.71 ± 71.83	36.80 ± 4.22	19.95** ± 1.69

Rats received s.c. injections of 5-methoxytryptophol (300 $\mu\text{g}/\text{day}/\text{rat}$) from 21 days of age for a period of 21 days. Values are means $\pm$ S.E.

† Number of animals in parentheses.

** $P < 0.001$.

ment, when treatment started at 30 days of age, 5-methoxytryptophol had no significant effect on the weight of the organs studied at either of the doses used, although a slight decrease in seminal vesicle and ventral prostate weights occurred in rats treated with the 300- μg dose (Table 3). From the results presented, it is evident that 5-methoxytryptophol displays a moderate inhibitory activity on the adnexal glands, which are structures under androgen control (Huggins, 1945). Furthermore, this inhibitory activity is seen only when pre-pubertal rats are used. Comparing the results of this experiment with the

TABLE 3
EFFECTS OF THE TREATMENT WITH 5-METHOXYTRYPTOPHOL ON SEXUAL
STRUCTURES OF MALE RATS

Treatment*	Final body weight (g)	Anterior pituitary weight (mg)	Testes weight (mg)	Seminal vesicle weight (mg)	Ventral prostate weight (mg)
Control (27)	131.48 ± 6.59	3.52 ± 0.18	1768 ± 80.70	84.88 ± 8.56	60.74 ± 5.99
5-Methoxytryptophol (100 µg/rat/day) (29)	132.44 ± 4.57	3.64 ± 0.16	1804.89 ± 69.16	75.20 ± 5.69	60.82 ± 4.54
5-Methoxytryptophol (300 µg/rat/day) (20)	129.66 ± 3.07	4.33 ± 0.15	1799.50 ± 31.24	68.66 ± 4.32	52.96 ± 2.85

Rats received treatment with 5-methoxytryptophol from 30 days of age for a period of 21 days. Values are means ± S.E.

* Number of animals on parentheses.

previous data obtained in our laboratory (Debeljuk, 1969), it is apparent that at similar dose levels, melatonin seems to be more effective as an inhibitory agent on the anterior pituitary and seminal vesicles. Moreover, younger rats seem to be more sensitive to 5-methoxytryptophol than older ones. This finding had been already observed in a previous report by Chu *et al.* (1964) studying the effects of melatonin. At present, no satisfactory explanation for this finding is available. It is possible that the brain structures related to gonadotrophic control are more sensitive to 5-methoxytryptophol at earlier ages, provided that this indole is able to cross the blood-brain barrier in sufficient amounts. The peripheral tissues involved in the inhibitory activity of 5-methoxytryptophol might also be more sensitive at earlier ages. Melatonin, which is structurally related to 5-methoxytryptophol, is able to exert inhibitory effects directly on the peripheral reproductive organs (Debeljuk, Feder & Paulucci, 1970b; Debeljuk, Vélchez, Schnitman, Paulucci & Feder, 1971). The possibility of a specific effect of 5-methoxytryptophol on pituitary FSH levels was recently proposed by Fraschini (1969). In the present report, no evidence of a selective inhibitory activity on the FSH-controlled sector could be detected, since the weight of the testes was not apparently affected by the treatment. The conditions of our experiment, however, differ considerably from those used by Fraschini (1969) and no definite conclusions on the possible mechanism of action of 5-methoxytryptophol can be reached at the present moment.

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