sterone (Ciba) (*5*) was injected into the inguinal region, at the dose of 20 μg/day in 0.2 ml of sesame oil.

For the quantitative assessment of inflammation, "granuloma-pouches" (*6*) were prepared 48 hr later by the injection of 25 ml of air under the dorsal skin; this was immediately followed by the injection of 0.5 ml of 1-percent croton oil (in corn oil) into the air space so created. All the animals were killed on the 14th day after adrenalectomy.

It is evident from Table 1 that, under these conditions, 20 μg of aldosterone slightly but significantly diminished the body-weight loss ($P < 0.01$) and the inhibition of inflammatory-exudate formation ($P < 0.01$) by cortisol. However, the involution of the thymus and spleen was not significantly suppressed.

A second experiment was therefore performed with a higher daily dose of aldosterone, but, in view of the scarcity of this hormone, the length of treatment had to be shortened. Thirty-six female Sprague-Dawley rats, weighing 154 to 163 g (average 160 g), were treated in essentially the same way as those of the first experiment, except that the granuloma-pouch was prepared on the first day, while treatment with steroids was begun 48 hr later, simultaneously with bilateral adrenalectomy. The dose of aldosterone was raised to 25 μg twice daily in 0.25 ml of sesame oil, and we added additional controls to which cholesterol (as an inactive steroid) and desoxycorticosterone acetate (Schering) (DCA, as a proved prophlogistic corticoid) were administered at the same dose level. For uniformity's sake, cortisol was also given in two daily subcutaneous injections (each 200 μg in 0.25 ml of water). The animals were killed on the 12th day.

Table 2 indicates that, at the dose level of 50 μg/day, aldosterone inhibits a variety of characteristic cortisol actions. In this respect it is approximately equally active as DCA. Cholesterol—a hormonally inert compound—is devoid of such an inhibitory action.

Depending upon the test used, the mineralocorticoid activity of aldosterone has variously been estimated to be about 25 to 125 times that of desoxycorticosterone (*7*). On the other hand, with regard to their anticortisol effects, we find no striking quantitative difference between the activities of the two steroids. It is noteworthy, however, that despite this the natural mineralocorticoid, aldosterone, inhibits all the afore-mentioned morphologic actions of the natural glucocorticoid, cortisol in the proportion 1:8.

Thus, the concept according to which a balance between two opposing naturally secreted corticoids can regulate the course of various biologic phenomena, including inflammation, has now been proved by direct experimental observations, using corticoids the presence of which in the circulating blood had been demonstrated beyond doubt (*8*).

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Gramine Derivatives Antagonistic to 5-Hydroxytryptamine (Enteramine)

V. Erspamer

Institute of Pharmacology, University of Bari, Bari, and *Farmitalia S.p.A. Research Laboratories, Milan, Italy*

It has been previously demonstrated that gramine (3-dimethylaminomethylindole) possesses, both *in vitro* and, to a lesser degree, *in vivo* a clear action antagonistic to 5-hydroxytryptamine (5-HT) (*1, 2*). In the present paper are briefly reported the main results obtained with nine gramine derivatives synthesized by Colò *et al.* (*3*) in the Farmitalia Research Laboratories.

The anti-5-HT activity of these derivatives was studied in respect to the spasmogenic effect of 5-HT on the rat estrous-uterus and to the antidiuretic effect of the substance in hydrated rats (*4*).

Table 1 shows the approximate dose of antimetabolite necessary to halve the uterus-stimulant effect produced by 0.1 μg of 5-HT base. For comparative purposes the values obtained with three of the most representative aminoindoles of Woolley and Shaw (*5*) are also included in the table: 2-methyl-3-ethyl-5-dimethylaminoindole (Medmain), 1,2-dimethyl-3-ethyl-

Table 1. Antagonistic effect of gramines and aminoindoles on the uterus-stimulant action of 5-HT.

Compound	50% antagonistic dose (μg) to 0.1 μg of 5-HT base
Gramine	3–6
2-Methylgramine	3–6
2-Methyl-5-aminogramine	200
2-Methyl-5-nitrogramine	3–5
2-Methyl-5-chlorogramine	0.3–0.4
2-Methyl-7-chlorogramine	0.5–0.8
2-Methyl-5-bromogramine	0.2–0.4
5,6-Dimethoxygramine	100
3-Diethylaminomethylindole	2–4
2-Methyl-3-pyperidylmethyl-5-chloroindole	4–8
Medmain	6–8
Methylmedmain	3–5
2-Methyl-3-ethyl-5-aminoindole	50–60

Table 2. Action of gramines and Methylmedmain on 5-HT antidiuresis.

Compound	Amount (mg/kg)	No. of rats	Percentage water excretion					
			1 hr	1½ hr	2 hr	3 hr	4 hr	7 hr
Controls (distd. water)		24	41	*63*	71	79	85	106
5-HT	0.2	24	13	26	37	*52*	60	84
5-Amino-2-methylgramine	10	12	35	*59*	62	73	82	102
5-Amino-2-methylgramine + 5-HT	10 + 0.2	12	12	23	36	*52*	65	98
5-Nitro-2-methylgramine	10	12	30	*51*	57	64	75	96
5-Nitro-2-methylgramine + 5-HT	10 + 0.2	12	9	18	22	41	*56*	82
5-Chloro-2-methylgramine	10	12	37	*53*	63	68	75	96
5-Chloro-2-methylgramine + 5-HT	10 + 0.2	12	18	42	*53*	59	63	83
Gramine	10	12	43	*59*	70	75	87	109
Gramine + 5-HT	10 + 0.2	12	29	41	*56*	64	66	87
Controls (distd. water)		12	39	*74*	77	86	98	118
5-HT	0.4	12	5	21	33	*54*	65	86
Methylmedmain*	20	12	48	*66*	82	84	88	111
Methylmedmain†	20	12	25	*52*	62	71	77	102
Methylmedmain* + 5-HT‡	20 + 0.4	12	10	29	40	*53*	61	86
Methylmedmain* + 5-HT§	20 + 0.4	12	2	10	22	44	*57*	88
Methylmedmain† + 5-HT‡	20 + 0.4	12	2	17	38	*54*	72	99
Methylmedmain† + 5-HT§	20 + 0.4	12	6	9	21	46	*54*	88

* By subcutaneous route.
† By intraperitoneal route.
‡ Injection of Methylmedmain 30 min before 5-HT.
§ Simultaneous injection of Methylmedmain and 5-HT.

5-dimethylaminoindole (Methylmedmain), and 2-methyl-3-ethyl-5-aminoindole. At the concentration used no stimulation of the uterine horn resulting from the antagonists for 5-HT was observed.

The inhibition caused by gramine derivatives is always, at least in part, reversible, but the original reactivity of the preparation is restored only gradually. It may even happen that after a first washing with fresh nutrient liquid the antagonistic effect is more pronounced than in the presence of the antimetabolite. The response of the rat uterus to acetylcholine is not significantly affected by the gramine compounds.

The antagonistic action on 5-HT antidiuresis of the drugs examined has always been rather weak and by no means proportional to their inhibiting action on the uterus-stimulant effect of 5-HT. None of the antimetabolites was superior to gramine in this respect but, at best, equal to it (*1*). This is true even for 2-methyl-5-chlorogramine. The action of the gramine derivatives seems to be more intense by subcutaneous route than by intraperitoneal route. Methylmedmain, like Medmain and 2-methyl-3-ethyl-5-aminoindole (*1, 4*), displays a negligible influence on 5-HT antidiuresis up to 20 mg/kg doses, whatever the route and time of administration may be.

Some experimental results concerning the influence of gramines and aminoindoles on 5-HT antidiuresis are summarized in Table 2. All the gramines were given subcutaneously 30 min before the water load (5 ml tap water per kg of body weight, by stomach tube), which was followed by subcutaneous injection of 5-HT; Methylmedmain was given by subcutaneous or by intraperitoneal route simultaneously with or 30 min before the water load and the injection of 5-HT. The attainment of approximately 50 percent water excretion is indicated by the figures in italic type.

Following intravenous injection of 1 to 10 mg/kg of 2-methyl-5-chlorogramine into a dog under pentobarbital anesthesia, both the pressor effect and the spasmogenic effect of 5-HT on the urinary bladder (*6*) are somewhat reduced but not abolished.

From these results we must conclude that while the anti-5-HT activity of some of the gramine derivatives studied appears to be very conspicuous when tested *in vitro* on the rat uterus preparation, the same activity is negligible when tested *in vivo* on the 5-HT antidiuresis test. It may be that this depends upon the rapid destruction of the drugs in the organism (*7*).

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