amounts of ecdysone are produced: each insect synthesizes up to 2 µg equivalent of pure ecdysone (average wet weight of a grasshopper at that time: 1 g).

2. The biosynthesis of ecdysone is a continuous process. Immediately after its synthesis, ecdysone is inactivated as a conjugate and possibly stored[9,10]. The rise of the moulting hormone titre on day 7 of the instar is caused by the activity of hydrolyzing enzymes. Experiments are under way to test these hypotheses.

Zusammenfassung. Der Titer von Ecdyson und Ecdysteron in Heuschrecken (*Locusta migratoria*) des V. Larvenstadiums wurde getrennt bestimmt. Ecdysteron herrscht zur Zeit des Titermaximums vor. Durch Injektion von radioaktivem Ecdyson wird gezeigt, dass dies durch ein Ansteigen der Steroid-20-Hydroxylase-Aktivität verursacht wird. Die Ausscheidung von Häutungshormonen mit dem Kot sorgt für das Sinken der Häutungshormon-Konzentration in den Tieren.

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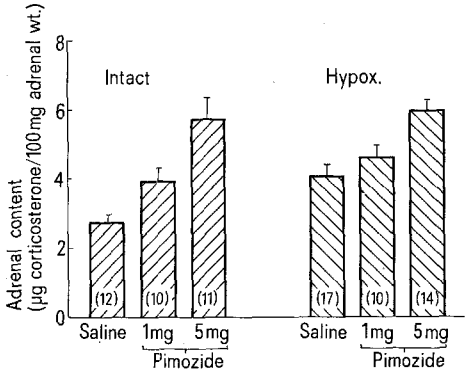
Effect of a Specific Dopaminergic Blocking Agent, Pimozide, on Hypothalamic Corticotropin-Releasing-Factor Activity in Rats: Clinical Correlates[1]

Recently attention has been focused on the effects of catecholaminergic mechanisms on the control of release and synthesis of hypophysiotrophic hormones[2,3]. This concept has become increasingly important with the widespread use of drugs affecting brain dopamine (DA) and norepinephrine (NE) and the large body of clinical evidence relating endocrine disorders to hypothalamic dysfunction[4,5].

For some years now, the neuroleptic Pimozide, a specific dopaminergic blocking agent, has been chronically administered to schizophrenic patients. Our recent clinical study with lipoatrophic diabetics (LD) has shown that the chronic administration of Pimozide (8 mg/day) causes a decrease in plasma corticotropin-releasing-factor (CRF) and a concomitant decrease in cortisol levels[6–8]. Since chronic treatment is indicated both in LD and in schizophrenia, it has become increasingly important to determine the effects of such drugs on the integrity of the hypothalamic-pituitary-adrenal axis. This report describes the effects of Pimozide on CRF activity in the median eminence of intact and hypophysectomized rats and its consequential effects on the integrity of the pituitary-adrenal axis.



ME-CRF content of intact and hypophysectomized rats treated with saline or 1 mg or 5 mg of Pimozide. CRF was estimated by changes in adrenal content in pharmacologically-blocked rats as outlined previously[9,11].

Materials and methods. 25-day-old female Sprague-Dawley rats were hypophysectomized and used 60 days later. Intact rats of the same age were used as controls. Rats (5–22/group) received saline, 1 mg or 5 mg Pimozide/rat i.p. for 7 days. On the 8th day the animals were sacrificed by decapitation and the median eminences (ME) were excised and homogenized in 0.1 *N* HCl (1 ml/ME). CRF assays were performed in pharmacologically-blocked rats by the method of Arimura et al.[9] but modifed by 12 min sampling and by estimation of adrenal content of corticosterone[10] as outlined in a previous study[11]. In this report, CRF activity is reported as increment in µg corticosterone per 100 mg adrenal weight. Plasma corticosterone was estimated using the fluorometric method of DeMoor et al.[12].

Results and discussion. CRF activity has been demonstrated to increase in the median eminence of rats after hypophysectomy[13]. In our study, administration of 1 mg or 5 mg Pimozide to hypophysectomized animals resulted in a further dose-related increase in ME-CRF (Figure).

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Effect of Pimozide on pituitary-adrenal function of intact female rat

Group	No. animals	Pituitary weight (mg)	No. animals	Resting levels (μgB/100 ml)	No. animals	Ether stress (μgB/100 ml)	No. animals	ACTH infusion (△μgB/100 mg adrenal wt.)
Untreated	14	12.93 ± 0.6	24	7.3 ± 0.8	22	61.3 ± 0.8	6	3.9 ± 0.5
Pimozide (1 mg/rat)	13	7.69 ± 0.3[a]	8	8.0 ± 0.6	22	62.4 ± 2.1	9	4.2 ± 0.6
Pimozide (5 mg/rat)	14	6.91 ± 0.5[a]	9	6.8 ± 0.7	10	53.5 ± 1.0[a]	6	3.2 ± 0.4

[a] $P < 0.01$ vs. untreated.

The administration of 1 mg or 5 mg Pimozide to intact animals resulted in even greater rise in ME-CRF activity than that seen in untreated hypophysectomized animals until levels were reached comparable to that found in the Pimozide-treated hypophysectomized rats. This increment in ME-CRF is interpreted as an inhibition of release of CRF and the elevated ME-CRF activity a reflection of accumulation rather than increased synthesis. Although CRF blood levels were not estimated directly, we make reference to the following studies to support this interpretation.

Pimozide inhibition of CRF release is substantiated by our previous clinical studies[8] that show plasma CRF and cortisol levels were decreased in LD patients who have been treated chronically with Pimozide. These same clinical studies als demonstrated that plasma luteinizing hormone releasing hormone (LRF) and luteinizing hormone (LH) were reduced in these patients further substantiating a generalized effect of the drug on inhibition of release of more than one hypothalamic releasing hormone. Analogous animal studies[14] have also shown a reduction in plasma LRF activity in hypophysectomized rats treated with Pimozide.

If release of CRF were not affected and the elevated ME-CRF were a reflection of increased synthesis, then the presence of increased ME-CRF should have caused increased secretion of pituitary ACTH and, consequently, increased peripheral corticosterone. This does not appear to be the case. The resting levels of adrenal corticosterone (Table) were not elevated. Pituitary weight decreased with increasing doses of Pimozide. Although pituitary hormone content was not estimated, one is tempted to speculate that pituitary ACTH likewise was reduced. A direct effect of Pimozide on pituitary ACTH is not ruled out in the intact animals but this is not a consideration in hypophysectomized rats.

The response to ether stress (Table), as measured by plasma corticosterone levels, was significantly decreased by 5 mg Pimozide. The response of the Pimozide-treated rats are reminiscent of rats bearing lesions in the median eminence that also show reduction in pituitary weight and inability to acutely respond to ether stress[15]. The reduction in pituitary weight in lesioned animals could be attributed to necrosis of pituitary tissue secondary to vascular infarction; in the Pimozide-treated animal this possibility is not a consideration. Infusions of exogenous ACTH showed that Pimozide-treated animals responded normally indicating no effect of the drug on adrenal sensitivity (Table).

Decrease pituitary ACTH concentration in the face of increased ME-CRF stores wou'd superficially present a dichotomy. However, if CRF could not reach the pituitary then the concomitant reduction in pituitary hormone would suggest that CRF may participate to some degree in the synthesis of pituitary ACTH. This hypothesis was previously suggested by UPTON and BRODISH[15]. It has been demonstrated that reduction in pituitary ACTH concentration[16,17] is not the limiting factor in the absence of stress-induced increases in blood ACTH. Therefore, the dampened ether stress response at the higher Pimozide dose must be due to a combination of impaired release of CRF and, consequently, reduced ability of the hypophysis to synthesize new ACTH rapidly enough for an acute response.

Since Pimozide specifically blocks dopamine, these studies suggest that a dopaminergic mechanism may be involved in the release of ME-CRF.

Résumé. L'administration du pimozide, un bloqueur spécifiquement dopaminergique, à des rats intacts et hypophysectomisés, a pour résultats une augmentation du CRF hypothalamique, une diminution concomitante du poids pituitaire ainsi qu'une réaction réduite à l'«ether stress». Ces données indiquent l'existence d'une mécanisme dopaminergique dans le contrôle de libération du ME-CRF.

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