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Corticosterone and prolactin response to TFMPP in rats during repeated antidepressant administration

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Abstract—The corticosterone and prolactin response to acute administration of the 5-HT agonist 1-(*m*-trifluoromethylphenyl) piperazine (TFMPP) (10 mg kg^{-1}) was assessed in rats treated for 10 days with either saline, amitriptyline (20 mg kg^{-1} day^{-1}) or nialamide (40 mg kg^{-1} day^{-1}). For all groups, TFMPP significantly increased both serum corticosterone and prolactin concentrations compared with control animals challenged with saline. However, the corticosterone response to TFMPP was attenuated significantly by nialamide pretreatment, while the prolactin response to TFMPP was enhanced significantly by amitriptyline pretreatment. These results support previous reports that antidepressants differentially affect 5-HT-ergic systems involved in the regulation of corticosterone and prolactin secretion.

Repeated antidepressant administration has been shown to affect the status of numerous transmitter systems in the brain (see Charney et al 1981; Sugrue 1983). Which of these changes, if any, are related to the clinical efficacy of antidepressants remains a focus of continued research. One neurotransmitter system which has been implicated in the pathophysiology of depression is 5-hydroxytryptamine (5-HT) (see Meltzer & Lowy 1987), and this system is frequently affected by chronic antidepressant administration, as evidenced by changes in responses elicited by activation of certain 5-HT receptor subtypes or by changes in the receptors themselves (see Frazer et al 1988).

In addition to behavioural and electrophysiological measurements, neuroendocrine responsivity has been used as a functional measure to assess alterations in 5-HT receptor-coupled responses induced by repeated administration of antidepressants. Studies in animals and man have shown that 5-HT regulation of the hypothalamic-pituitary-adrenal (HPA) axis and prolactin secretion is modified markedly by antidepressant treatment (Meltzer et al 1981; Price et al 1985; Aulakh et al 1988a, b, 1989). These studies have shown that the prolactin response to a variety of 5-HT agonists is consistently enhanced. To expand upon this body of data, and further assess the consistency of these findings, the present study was undertaken using an antidepressant drug and a 5-HT receptor agonist not employed previously in such studies.

Materials and methods

Male Sprague Dawley rats (Ace Animals, Boyertown, PA), 250–300 g, were housed in group cages in a temperature and humidity controlled room illuminated 12 h day (lights on at 0630 h). Rats had free access to food and water. Seven days after arrival, animals were injected intraperitoneally (i.p.) with either 0·9% NaCl (saline), amitriptyline (10 mg kg^{-1}) or nialamide (20 mg kg^{-1}) (both obtained from Sigma Chemical Co., St Louis, MO) twice daily for 10 days. Twenty-four hours after the last injection, animals were challenged i.p. with saline or with a submaximal dose (Fuller & Clemens 1979; Poland & Frazer unpublished) of 1-(*m*-trifluoromethylphenyl)piperazine (TFMPP) (10 mg kg^{-1}) (Aldrich Chemical Co., Milwaukee, WI) and decapitated 1 h later.

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Trunk blood was collected for the measurement of serum corticosterone and prolactin concentrations by radioimmunoassay as described previously (Poland et al 1980, 1981). Prolactin concentrations are presented as RP-1 values. All samples for each hormone were analysed in the same assay. As determined by multiple serum pool replicates analysed in each assay, maximum intra-assay variability was 9·7% for both hormones. Data were analysed by *t*-tests with significance levels corrected for multiple comparisons (Jacobs 1976).

Results

In a preliminary study, we found that by 1 h both the corticosterone and prolactin responses to a saline injection returned to baseline values. Therefore subsequent experiments were carried out using this time point. The corticosterone and prolactin concentrations after acute saline injection (Fig. 1) were similar for all three groups with values comparable to those measured in non-injected, non-treated animals (Poland et al 1980). Compared with acute saline administration, the acute injection of TFMPP significantly increased both serum corticosterone ($P < 0.001$) and prolactin ($P < 0.001$) concentrations in all animals, irrespective of their pretreatment regimen.

As shown in Fig. 1A, treatment of rats for 10 days with amitriptyline did not affect the corticosterone response to acute injection of TFMPP. However, the corticosterone response to TFMPP was reduced significantly by sub-chronic administration of nialamide ($P < 0.01$). By contrast, the prolactin response to TFMPP was enhanced by treatment with amitriptyline ($P < 0.01$), whereas nialamide treatment did not affect the prolactin response to TFMPP (Fig. 1B).

Discussion

TFMPP has been found to stimulate both corticosterone and prolactin secretion in a dose-dependent fashion (Fuller & Clemens 1979). Although TFMPP has been reported to bind with high affinity to numerous 5-HT receptor subtypes, its greatest affinity appears to be for 5-HT_{1B} and 5-HT_{1C} subtypes (Glennon 1987; Hoyer 1988). However, in spite of its high affinity to 5-HT receptors, the corticosterone response to TFMPP cannot be blocked by metergoline pretreatment (Fuller & Snoddy 1979). Thus, the 5-HT receptor subtype(s) on which it acts to produce its neuroendocrine responses is unclear. In the present study, TFMPP also stimulated corticosterone and prolactin secretion, responses which were differentially modulated by exposure to a 10 day regimen of antidepressant treatment. The prolactin response to TFMPP was enhanced by amitriptyline and the corticosterone response was attenuated by nialamide.

Previous studies in rats have shown that the prolactin response to the non-selective, indirectly acting 5-HT agonist 5-hydroxytryptophan was enhanced in animals treated repeatedly with either imipramine or desmethylimipramine (Meltzer et al 1981). Similarly, the prolactin response to 8-hydroxy-2-(di-n-propylaminon tetrali) (8-OH-DPAT), a selective 5-HT_{1A}-agonist, was enhanced by repeated clomipramine pretreatment

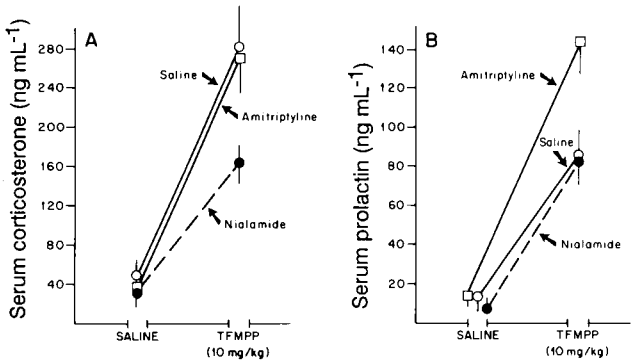

FIG. 1. Effects of saline, amitriptyline (20 mg kg^{-1} day^{-1}) and nialamide (40 mg kg^{-1} day^{-1}) on serum corticosterone and prolactin concentrations. Rats (n = 8) were treated with saline or with antidepressants for 10 days. Twenty-four hours after the last treatment, animals were injected with saline or TFMPP (10 mg kg^{-1}) and blood samples were obtained 1 h later.

(Aulakh et al 1988b). In man, chronic amitriptyline, desmethylimipramine or fluvoxamine treatment has been shown to increase the prolactin response to tryptophan in adult depressives (Price et al 1989a, b). Thus, these results, coupled with the TFMPP responses, suggest that multiple subtypes of 5-HT receptors or 5-HT receptor-coupled responses are affected by repeated exposure to antidepressants, with the net functional effect being enhanced responsivity, as manifested by a greater prolactin response to 5-HT agonist challenges. Whether it is the amine reuptake inhibitory activities and/or the potent 5-HT receptor antagonist properties (Peroutka & Snyder 1980; Hyttel & Larsen 1985) of these compounds which are responsible for the change in status of 5-HT systems remains to be determined. In contrast to the effects of such antidepressants on prolactin secretion, the corticosterone response elicited by 8-OH-DPAT was unaffected by imipramine or clomipramine pretreatment (Aulakh et al 1988b), as is the corticosterone response to TFMPP following amitriptyline treatment as reported herein.

The adaptive changes of neuroendocrine regulation following monoamine oxidase inhibitor (MAOI) administration are less consistent than for reuptake inhibitors. Chronic treatment with clorgyline significantly attenuated the prolactin response to 8-OH-DPAT and to *m*-chlorophenylpiperazine (MCPP) (Aulakh et al 1988a, b) the latter compound being a 5-HT agonist whose properties are similar to those of TFMPP, both in-vivo (Schechter 1988; Kennett & Curzon 1988) and in-vitro (Hoyer 1988; Schoeffter & Hoyer 1989). However, the administration of the less selective MAOI, nialamide, did not affect the prolactin response to TFMPP. Similarly, tranylcypromine, another non-selective MAOI, did not enhance the peak prolactin response to tryptophan challenge in man (Price et al 1985).

With regard to the HPA axis, clorgyline has been reported not to affect the corticosterone response to MCPP or 8-OH-DPAT (Aulakh et al 1988a, b), but our data indicate that nialamide significantly reduced the corticosterone response to TFMPP. It is possible that the non-selectivity of nialamide, coupled with the relatively non-selective 5-HT effects of TFMPP, could account for the differential findings. If this were so, nialamide might be expected to manifest an effect on 5-HT systems even if other 5-HT subtype selective agonists, such as 8-OH-DPAT or 1-(2,5-dimethoxy-4-iodo-phenyl)-2-aminopropane (DOI), were used as probes. Conversely, if clorgyline was administered instead of nialamide, an attenuated corticosterone response to TFMPP might be expected not to occur.

Evidence suggests that 5-HT systems projecting from the dorsal raphe to the hypothalamus mediate prolactin secretion while other 5-HT systems control the HPA axis (Van de Kar & Lorens 1979; Van de Kar & Bethea 1982; Van de Kar et al 1985). Since all of the tricyclic antidepressants studied thus far affect 5-HT control of prolactin, it is conceivable that these drugs work predominantly on 5-HT systems emanating from the dorsal raphe. The lack of effect of tricyclics on 5-HT projections controlling the HPA axis suggests that not all 5-HT systems are affected in a similar fashion. Alternatively, because it has been shown that 5-HT-induced prolactin changes are mediated, at least in part, through a dopaminergic pathway (Tuomisto & Mannisto 1985), it is possible that the antidepressant-induced changes in prolactin caused by 5-HT activation are actually the reflection of an alteration in hypothalamic dopaminergic projections, an issue discussed recently (Poland 1990). As to why clorgyline affects the 5-HT regulation of prolactin, while nialamide does not, remains unclear.

In summary, neuroendocrine regulation by 5-HT systems is markedly affected by the administration of some antidepressants. However, the mechanisms underlying these regulatory changes are unclear. Whether such changes in 5-HT status are reflective of a mechanism which also underlies the clinical efficacy of antidepressants remains to be determined. Additional studies utilizing different classes of antidepressants and selective 5-HT probes would be of interest.

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Inhibition of [^{3}H]dopamine uptake by platelets by the dopamine-D_2 receptor agonist RU 24926

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Abstract—We have examined the effect of the dopamine-D_2 receptor agonist RU 24926 (*N*-n-propyl-di-β(3-hydroxy-phenyl)-ethylamine HCl) on [^{3}H]dopamine uptake by human platelets. RU 24926 reduced the uptake of [^{3}H]dopamine by platelet-rich plasma and this affect was not reversed by the dopamine-D_2 receptor antagonist haloperidol, or the dopamine-D_1 receptor antagonist SCH 23390 (8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol). These data suggest that RU 24926 reduces [^{3}H]dopamine uptake by platelets by competing for the dopamine uptake mechanism on the platelet and not by activation of the dopamine-D_2 receptor.

Dopamine uptake by human platelets has been shown to be by an energy and temperature process (Solomon et al 1970; Dean & Copolov 1989) which does not involve binding to the dopamine-D_1 or D_2 receptor (Dean & Copolov 1989). To determine if activation of the D_2 receptor could modulate uptake by platelets we have examined the effect of the D_2 receptor agonist, RU 24926 (Euvard et al 1980), on the uptake of [^{3}H]dopamine by human platelets.

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Materials and methods

The studies were approved by the human ethics committee of Royal Park Hospital, and the volunteers gave written, informed consent.

[^{3}H]Dopamine uptake by platelets was measured as described previously (Dean & Copolov 1989). Blood was obtained from volunteers selected at random from 59 individuals. At the time of donation the volunteers had no current medical problems and had not taken drugs for at least three weeks. Platelet rich plasma (PRP) was taken as the supernatant after centrifuging the blood, which had been anti-coagulated with EDTA, at 100 *g* for 15 min.

Samples of PRP (250 μL) were incubated with a range of concentrations of unlabelled dopamine or RU 24926 (0–10 μM)