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Chronic antidepressant treatment increases the apomorphine-induced elevation of plasma corticosterone in rats

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Abstract—Plasma corticosterone concentrations in response to subcutaneous administration of apomorphine (25 and 200 $\mu g\ kg^{-1}$) have been assessed in rats treated acutely (2 days) or repeatedly (15 days) with saline, clomipramine, electroshock and clomipramine + electroshock. Chronic, but not acute, antidepressant treatment decreased the corticosterone level which remained unchanged in control and in rats acutely treated with apomorphine. Chronic antidepressant treatment significantly increased the corticosterone response to apomorphine. Neuroendocrine evidence is provided for an increased responsiveness of dopamine receptors which are thought to mediate the apomorphine effect on corticosterone secretion following chronic antidepressant treatment.

Numerous reports have substantiated the role of central dopamine (DA) systems in depression and in the mechanism of antidepressant (AD) agents (Willner 1983a, b). Several publications suggested decreased sensitivity to the behavioural, biochemical and electrophysiological effects of drugs stimulating presynaptic DA receptors after long term AD treatment (Serra et al 1979; Chiodo & Antelman 1980). Moreover, responses mediated via activation of postsynaptic DA receptors also appear to be enhanced after chronic AD treatment (Green et al 1977; Delini-Stula & Vassout 1979; Spyraki & Fibiger 1981; Maj et al 1984; Spyraki et al 1985). It is well established that centrally acting DA agonists increase the corticosterone concentration in rats (Fuller & Snoddy 1981). This effect appears to be mediated by central DA receptors of the D_2 subtype, which are located postsynaptically (Creese et al 1983).

The issue addressed herein is whether chronic AD treatment-induced modifications of central DA receptor function attributed to the nigrostriatal, mesolimbic and mesocortical DA systems, also concern the tuberoinfudibular DA system. Investigations dealing with receptor activity modifications of the tuberoinfudibular system are of interest, inasmuch as many pathophysiological correlates of a depressive illness are subject to or are associated with regulatory disturbances in neuroendocrine function.

Materials and methods

Male albino Wistar rats (reared in our laboratory), 250 g at the start of the experiment, were housed 8 per cage and maintained on a controlled 12 h light/dark cycle, with access to food and water. For each study (acute and chronic treatment) animals were divided into four groups, of 27 animals each, receiving the following treatment: (0·9% NaCl saline); clomipramine HCl (CMI 5·0 mg kg^{-1}, Ciba-Geigy); electroshock (ECS); and CMI + ECS. The last group was included because we have recently found that ECS attenuates the effect of CMI on specific DA systems (Spyraki et al 1985). In the acute treatment studies animals were treated for two days and in the chronic treatment studies for two weeks. Injections were given to rats i.p., twice a day (0800 and 2000 h). ECS was administered to rats through ear-clip electrodes. The current (150 mA, 50 Hz, 0·3 s) invariably produced clonic and in most cases tonic, seizures of approximately 20 s duration. No deaths occurred. The rats in the ECS and CMI + ECS groups received either one shock (acute treatment) or a series of eight treatments at 48 h intervals (chronic spaced treatment). Shocks were given at 12 00–13 00 h. Saline and CMI-treated rats were handled similarly but no current was passed.

Four days after withdrawal from either the 2 or 15 day regimens and between 1200–1500 h, the animals were challenged with either vehicle (saline containing ascorbic acid, 0·2 mg mL^{-1}) or apomorphine (25 or 200 $\mu g\ kg^{-1}$ s.c.). Thirty minutes later, following decapitation, blood was collected from the neck blood vessels into K 3 EDTA-containing vials. Specimens were immediately centrifuged at 4°C the plasma was collected and stored at −20°C until analysed.

Plasma corticosterone (PC) was determined by dextran coated radioimmunoassay, following extraction of corticosterone with ether. Rabbit anticorticosterone-3-BSA was supplied by Cambridge Medical Diagnostic Inc. The results were analysed statistically using two-way analysis of variance. Student's *t*-test was also employed for individual comparisons.

Results

The data in Fig. 1 show that chronic administration of AD treatments significantly ($P < 0·02$) decreased PC levels. Furthermore, the results indicate that apomorphine, at both doses tested, did not induce elevation of PC levels in control (saline) animals. This is in accordance with the Fuller & Snoddy (1981) report which showed that doses of apomorphine higher than 1 mg kg^{-1} i.p. are required to induce significant increases in PC levels. We have obtained similar results in pilot dose-response (apomorphine- corticosterone) studies. However, apomorphine at 25 and 200 $\mu g\ kg^{-1}$ doses thought to stimulate pre- and postsynaptic DA sites, respectively, induced PC elevation in rats receiving various chronic AD treatments. Analysis of variance indicated a significant overall difference between chronically treated groups ($P < 0·01$) and a significant effect of apomorphine ($P < 0·01$). A significant dose × group interaction was also revealed ($P < 0·01$). This is probably due to the lower PC baseline (vehicle injected) levels of chronic AD-treated animals compared with controls and with the fact that apomorphine, although ineffective in control animals, did induce PC elevation in experimental rats.

In contrast to the marked increase of the apomorphine effect on corticosterone secretion after chronic AD administration, acute AD treatment did not influence the effect of apormorphine (200 $\mu g\ kg^{-1}$, s.c.) on PC levels (Table 1).

Table 1. Plasma corticosterone ($\mu g\ dL^{-1}$) 30 min following s.c. administration of apomorphine in rats acutely (2 day) after antidepressant treatment.

	Controls	CMI	ECS	CMI + ECS
Vehicle	8·75 ± 0·9	9·35 ± 1·3	8·85 ± 0·9	7·87 ± 1·0
Apomorphine HCl (200 $\mu g\ kg^{-1}$)	9·08 ± 0·6	7·89 ± 0·8	8·67 ± 0·6	8·84 ± 0·7

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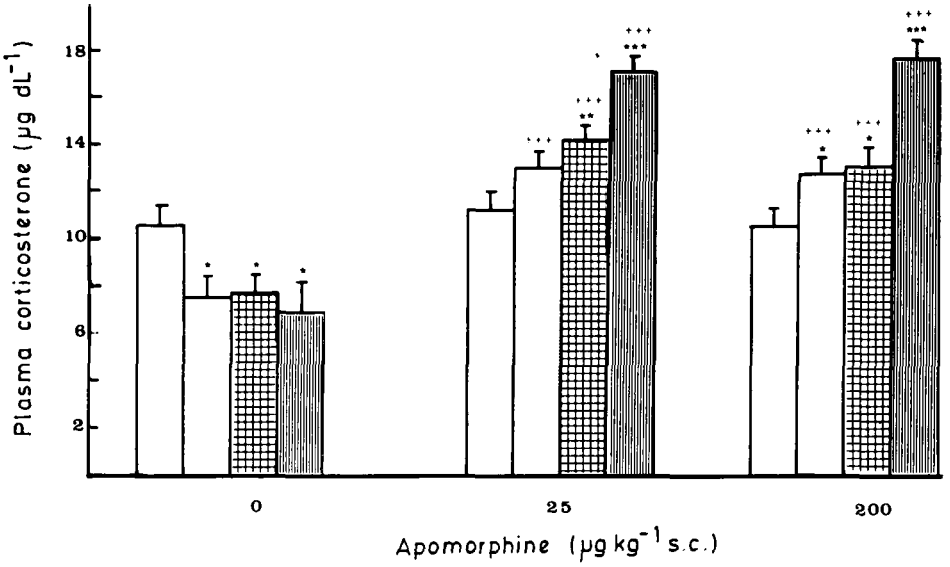

FIG. 1. The effect of chronic antidepressant treatment on apomorphine-induced elevation of plasma corticosterone. Data represent means (±s.e.m.) of 9 animals/group. Significantly different from respective control groups (saline treatment): $^{*}P<0.02$; $^{**}P<0.01$; $^{***}P<0.001$. Significantly different from respective vehicle treated groups: $^{+++}P<0.001$. 1st column = saline. 2nd column = clomipramine. 3rd column = electroshock. 4th column = clomipramine + electroshock.

Discussion

Our results are in agreement with the well established functional evidence indicating that chronic AD treatment increases the responsiveness of postsynaptic DA receptors (see Introduction). Thus, the elevation of PC levels following administration of apormophine is seen in rats chronically, but not acutely, treated with the different AD treatments.

Several facts suggest that the neuroendocrine findings obtained in the present experiments are due to central postsynaptic DA receptor stimulation. Specifically, it is known that the apomorphine effect on PC elevation is mediated by central postsynaptic receptors as the effect is blocked by haloperidol but not domperidone; it is also elicited by agents that preferentially stimulate D_2 receptors (Fuller & Snoddy 1981) and there is strong evidence that the D_2 receptors are postsynaptic in location (Creese et al 1983). Although D_2 receptors are also found in presynaptic terminals (Kebabian & Calne 1979; Breese et al 1987), it has been claimed that the tuberoifudibular DA system, which regulates the hypothalamo-pituitary-adrenal axis at least in part, lacks presynaptic DA receptors (Andén et al 1983). The fact that in our study a presynaptically acting dose of apomorphine (25 μ kg^{-1}, s.c.) induced corticosterone secretion in chronic AD-treated rats may be due to change in dose specificity, because of chronic treatment with AD induced hyperesponsive postsynaptic DA sites.

Neuroendocrine evidence for increased responsiveness of DA receptors following chronic electroconvulsive therapy has been reported for both animals and man (Balldin et al 1982). In those studies growth hormone secretion and prolactin suppression, following apomorphine, were used as hormonal models to investigate receptor sensitivity. Our study using a third hormonal model, apomorphine-induced corticosterone secretion, presents results consistent with the above studies. Therefore, it appears that the development of supersensitive postsynaptic DA receptors following ECS is a robust phenomenon and perhaps common to different antidepressant treatments. This latter assumption derives from the fact that similar results were obtained with chronic CMI and CMI + ECS, treatments which have been shown to differentially influence mesolimbic/mesocortical DA systems-mediated functions (Spyraki et al 1985).

Of interest seems to be the observation that chronic, but not acute, AD treatment decreased the baseline levels of PC. It could be assumed that this is due to everyday handling of animals (in contrast to acute treatment) that probably works to cancel out stress-inducing factors upon which ACTH release depends. However, rats in the acute treatment groups did not have higher PC levels than the chronic saline group, which in addition was handled similarly to the chronic AD groups. A more plausible explanation appears to be the conjecture that chronic AD treatment reduces the subject's ability to experience stressful situations, thus elevating the threshold of the HPA axis response. Whatever its basis, our observation that chronic AD treatment induced decrease in PC levels, would correlate well with the restoration to normal values of the increased plasma cortisol concentration in depressed patients whose condition is improved by AD therapy (Sachar 1982).

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References

Andén, N.-E., Grabowska-Andén, M., Liljenberg, B. (1983) J. Neural Transm. 57: 129–137
Balldin, J., Granerus, A. K., Lindestedt, G., Modigh, K., Wålinder, J. (1982) Psychopharmacology 76: 371–276
Breese, G. R., Duncan, G. A., Napier, T. C., Bondy, S. C., Iorio, L. C., Mueller, R. A. (1987) J. Pharmacol. Exp. Ther. 240: 167–176
Chiodo, L. A., Antelman, S. M. (1980) Eur. J. Pharmacol. 64: 203–204
Creese, I., Sibley, D.R., Hamblin, M. W., Leff, S. E. (1983) Ann. Rev. Neurosci. 6: 43–71
Delini-Stula, A., Vassout, A. (1979) Eur. J. Pharmacol. 53: 443–451
Fuller, R. W., Snoddy, H. D. (1981) Endocrinology 109: 1026–1032
Green, A. R., Heal, D. J., Grahame-Smith, D. G. (1977) Psychopharmacology 52: 195–200
Kebabian, J. W., Calne, D. B. (1979) Nature 277: 93–96
Maj, J., Rogoz, Z., Skuza, G., Sowinska, H. (1984) J. Pharm. Pharmacol. 36: 127–130
Sachar, E. J. (1982) in: E.S., Paykel (ed.) Handbook of Affective Disorders, Churchill Livingstone, pp 191–201
Serra, G., Argiolas, A., Klimek, V., Fadda, F., Gessa, G. L. (1979) Life Sci. 25: 415–424
Spyraki, C., Fibiger, H. C. (1981) Eur. J. Pharmacol. 74: 195–206
Spyraki, C., Papadopoulou, Z., Kourkoubas, A., Varonos, D. (1985) Naunyn-Schmiedeberg's Arch. Pharmacol. 329: 128–134
Weilosz, M. (1981) Neuropharmacology. 20: 941–945
Willner, P. (1983a) Brain Res. Rev. 6: 211–224
Willner, P. (1983b) Ibid. 6: 237–246.