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ORIGINAL INVESTIGATION

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Effects of adrenalectomy on 8-OH-DPAT induced hypothermia in mice

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Abstract Complex interactions exist between the hypothalamic-pituitary-adrenal (HPA) axis and the serotonergic system, and it has been suggested that these interactions may be fundamental to the pathophysiology and treatment of depressive illnesses. It has previously been found that chronic administration of corticosterone leads to adrenal suppression and an attenuation of somatodendritic 5-HT_{1A} receptor function. Adrenalectomy (ADX) has been shown to cause an increase in postsynaptic 5-HT_{1A} receptor numbers and possibly function. However, other reports have suggested that ADX does not alter somatodendritic 5-HT_{1A} receptor mRNA or binding, though little is known of the effect of ADX on the function of somatodendritic 5-HT_{1A} receptors. This study investigated the effect of markedly reducing corticosterone levels by ADX on 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT)-induced hypothermia in mice, an in vivo model of somatodendritic 5-HT_{1A} receptor function. The degree of 8-OH-DPAT-induced hypothermia did not differ between control, sham, and ADX animals 14 days post operatively. Although repeated administration of corticosterone attenuates somatodendritic 5-HT_{1A} receptor function, these data demonstrate that lowering of corticosteroid levels by ADX have no effect. This suggests that the effects of repeated corticosterone administration is not mediated by a secondary adrenal suppression. The difference in the effects of ADX on somatodendritic as opposed to postsynaptic 5-HT_{1A} receptors may reflect the differential expression of corticosteroid receptor subtypes at postsynaptic and somatodendritic sites.

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Introduction

Complex interactions have been described between the serotonergic system and the HPA axis and changes in corticosteroid levels have been shown to exert profound effects on 5-HT levels, receptor numbers and functional responses (Chaouloff 1993). Changes in the serotonergic system as a result of alterations in HPA axis activity may be of physiological relevance, and it has been postulated that disruption of serotonergic-HPA axis interactions is central to the pathophysiology of depression (McAllister-Williams et al. 1998). 5-HT_{1A} receptors are particularly important in serotonergic-HPA axis interactions (Chaouloff 1993; McAllister-Williams and Young 1998). These receptors are located both postsynaptically and on the soma and dendrites of raphé serotonergic neurones. Postsynaptic 5-HT_{1A} receptors are believed to be important in adaptive mechanisms to aversive stimuli, and it has been suggested that disruption of transmission through these receptors may lead to a depressive illness (Deakin and Graeff 1991). This hypothesis is supported by several studies showing an impairment of postsynaptic 5-HT_{1A} functional responses in depressed subjects (reviewed by Power and Cowen 1992). Activation of somatodendritic 5-HT_{1A} receptors decreases the firing of raphé neurones and hence the activity of the entire serotonergic system. To date, it has not been possible to examine the functional activity of these receptors directly in depressed patients. However, studies in rodents suggest that antidepressants may act by attenuating the function of these 5-HT receptors (Goodwin et al. 1985; Blier and deMontigny 1994).

Numerous studies have shown that ADX in rodents causes an increase in postsynaptic 5-HT_{1A} receptors (Mendelson and McEwen 1992; Chalmers et al. 1993, 1994; Kuroda et al. 1994; Tejani-Butt and Labow 1994; Zhong and Ciaranello 1995; Burnet et al. 1996; Aguirre et al. 1997) and that this is reversed by corticosterone (Mendelson and McEwen, 1992; Chalmers et al. 1993; Meijer and de Kloet 1994, 1995; Tejani-Butt and Labow 1994). It is unclear if this effect of ADX on postsynaptic 5-HT_{1A} receptor numbers is mirrored by changes in the function of the receptor, although one study has demonstrated that 8-OH-DPAT-induced hypothermia in rats, a response that may partially reflect postsynaptic 5-HT_{1A} receptor activation (Bill et al. 1991), is enhanced by ADX (Young et al. 1993).

A number of groups have suggested that ADX does not lead to the increase in somatodendritic 5-HT_{1A} receptors that is seen at the postsynaptic site (Laaris et al. 1995; Aguirre et al. 1997; Le Corre et al. 1997). However in vivo studies utilising 8-OH-DPAT-induced hyperphagia in rats, (Haleem 1992) and 8-OH-DPAT-induced hypothermia in rats and mice (Young et al. 1992, 1994) as models of 5-HT_{1A} receptor function, suggest that corticosterone administration attenuates somatodendritic 5-HT_{1A} function. This suggestion is supported by data from a single electrophysiological study in rats (Laaris et al. 1995). However, the mechanism of this attenuation of function is unclear. Although animals received large doses of corticosterone, at the time of testing serotonergic function, their plasma corticosterone levels were in fact low (15.9 ng/ml; Young et al. 1994). This suggests that the exogenous corticosterone had led to adrenal suppression. It is therefore unclear as to whether the attenuation of somatodendritic 5-HT_{1A} receptor function that occurs secondary to corticosterone administration is as a result of several "pulses" of hypercortisolaemia over a period of time, or hypocortisolaemia at the time of testing. The present study was designed to clarify this point by investigating the effect of ADX on somatodendritic 5-HT_{1A} receptor function. We utilised an in vivo model of somatodendritic 5-HT_{1A} function, 8-OH-DPAT induced hypothermia in mice (Bill et al. 1991; Martin et al. 1992).

Materials and methods

Animals

Adult male Balb-C normal strain mice (University of Newcastle-upon-Tyne Animal House), weighing 25–30 g, were housed individually under conditions of controlled temperature (20–22°C), humidity (45%), and lighting (12-h light/dark cycle). Food pellets and water were freely available. Animals were reared, and all experimental procedures carried out, under British Home Office guidelines laid down in the Animals (Scientific Procedures) Act, 1986.

Adrenalectomy

Mice were anaesthetised with isoflurane. A small 1 to 2-cm midline skin incision was made to the dorsal surface just below the start of the rib cage. Two small incisions were made to the muscle wall either side of the spinal column to allow visualisation of the adrenal glands, which were removed using blunt forceps. Sham-operated mice underwent the same procedure but the adrenal glands were only visualised. Incisions were closed with sutures.

Drugs

8-Hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) was obtained from Sigma, Poole, UK, made up in 0.9% saline, and administered subcutaneously. The dose (0.5 mg/kg) used was as in previous studies and represents the mid-point of the dose-response curve for the hypothermic response (Young et al. 1994).

Temperature

8-OH-DPAT hypothermic challenge tests were performed 14 days post-ADX. Temperature was measured by inserting a lubricated probe 2 cm into the rectum with the animals loosely restrained, with readings displayed on a digital thermometer. Recordings were made 10 min and immediately before the 8-OH-DPAT challenge (0.5 mg/kg) was administered, giving two baseline readings which were averaged. Recordings were subsequently made at 10, 20 and 30 min post-injection of challenge agent. After all temperature readings were taken, the animals were killed by neck dislocation. All testing was carried out between 0900 hours and 1100 hours.

Corticosterone measurement

Following the hypothermia challenge, the animals were decapitated and bled. Blood was collected and serum obtained and stored at −2°C for later analysis. Corticosterone levels were assayed using radioimmunoassay kits supplied by Immuno Diagnostic Systems Ltd, Boldon, Tyne and Wear, UK. Intra- and inter-assay coefficients of variation were 5.4% and 8.6%, respectively.

Statistics

SPSS for Windows release 7 (SPSS, Chicago, Ill., USA) was used for statistical analysis. The hypothermia data was analysed using a two-way analysis of variance (ANOVA) with treatment (ADX, sham ADX or control) and time as the main variables. In addition, temperature changes were also assessed by calculating the area under the curve (AUC) for the three time points post-hypothermic challenge, relative to the average baseline measurement, using the trapezoid method. AUCs for animals given the same treatments were averaged and compared with alternative treatments using the Mann-Whitney test. Corticosterone levels in differing groups of animals were compared using a two-tailed Student *t*-test. The correlation between corticosterone levels and AUC results from individual animals was analysed using the Pearson correlation coefficient. Two-tailed tests of significance were applied. Results are reported as means ±SE.

Results

Twenty-six mice underwent ADX. The hypothermia results from eight were excluded because they had

corticosterone levels greater than 100 ng/ml, suggesting incomplete ADX. The remaining 18 mice had an average corticosterone level of 48.6 ± 2.8 (range: 31.1 −75.6), significantly lower than the corticosterone level in both sham ADX animals (625.0 ± 51.2, range: 458.4–970.8, $n = 11$, $P < 0.0001$) and control mice that simply underwent the hypothermia challenge (746.7 ± 49.5, range: 432.5–1125.9, $n = 14$, $P < 0.0001$). A non-significant trend towards reduced corticosterone levels in sham ADX animals compared to controls was seen ($P = 0.06$).

ANOVA showed a highly significant effect of time ($F = 94.9$; $df = 4,200$; $P < 0.0001$) but no effect of group ($F = 0.13$; $df = 2,200$; $P = 0.879$) or group by time interaction ($F = 0.12$; $df = 8,200$; $P = 0.999$) on the hypothermic response to 8-OH-DPAT (Fig. 1). Post-hoc comparison of mean AUC also showed no significant difference between the hypothermia induced by 8-OH-DPAT in ADX (54.2 ± 6.4), sham ADX (63.1 ± 6.9) and control animals (58.2 ± 7.4). The AUC data was also examined for a correlation with the corticosteroid levels in individual animals (Fig. 2). No significant correlation was found in ADX ($r = 0.25$, $P = 0.32$), sham ADX ($r = 0.54$, $P = 0.09$) or control animals ($r = 0.0004$, $P = 0.99$). This was also the case when the data from all of the animals was combined ($r = 0.16$, $P = 0.31$).

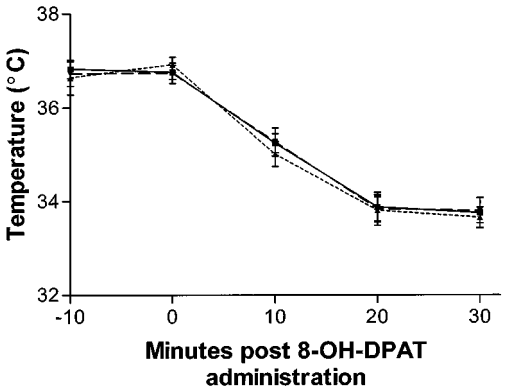

Fig. 1 Effects of 0.5 mg/kg 8-OH-DPAT on body temperature of mice following ADX (■), sham ADX (▲) or no surgical procedure (▼ controls). 8-OH-DPAT was administered at time 0. Points plotted are the means ±SE for 18, 11 and 14 animals, respectively

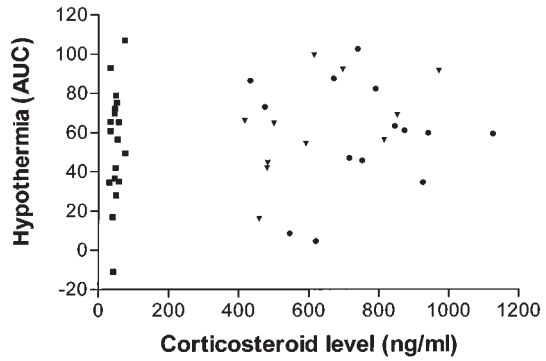

Fig. 2 AUC values for 8-OH-DPAT-induced hypothermia plotted against corticosteroid levels for individual animals. ■ ADX, ▼ sham ADX, ● controls

Discussion

The main finding of this study is that ADX does not effect the hypothermic response to 8-OH-DPAT in the mouse. This response is believed to be a model of somatodendritic, as opposed to postsynaptic, 5-HT_{1A} receptor function, since the serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) completely abolishes it in mice (Bill et al. 1991; Martin et al. 1992). This is not the case in rats, where the effect appears to be mediated to a large extent by postsynaptic 5-HT_{1A} receptors (Bill et al. 1991). It is possible that this reflects differential distribution of 5-HT_{1A} receptors in rodents. For example, in rats, the highest levels of 5-HT_{1A} receptors in hippocampus are found in the dentate gyrus with moderate levels in the CA1 region (Wright et al. 1995). However, in the mouse highest levels of the receptor and receptor mRNA are found in CA1 with low levels in the dentate gyrus (Laporte et al. 1994).

The findings of this study contrast with the previous study in rats demonstrating that ADX enhances 8-OH-DPAT induced hypothermia (Young et al. 1993). The most parsimonious explanation of the differing effects of ADX in rats is the involvement of postsynaptic receptors. No effect of ADX is seen on presynaptic somatodendritic 5-HT_{1A} receptor mRNA or binding on rat raphé serotonergic neurones (Laaris et al. 1995; Aguirre et al. 1997; Le Corre et al. 1997). In addition, electrophysiological studies in rats show that ADX does not effect either the spontaneous firing rate of raphé neurones or the reduction in firing rate mediated by activation of 5-HT_{1A} receptors with the specific agonist 8-OH-DPAT (Laaris et al. 1995). This is in contrast to the well documented findings that ADX in rats increases postsynaptic 5-HT_{1A} receptor mRNA (Chalmers et al. 1993, 1994; Meijer and de Kloet 1994, 1995; Zhong and Ciaranello 1995; Burnet et al. 1996; Aguirre et al. 1997; Le Corre et al. 1997) and 5-HT_{1A} binding sites (Mendelson and McEwen 1992; Chalmers et al. 1993, 1994; Kuroda et al. 1994; Tejani-Butt and Labow 1994; Zhong and Ciaranello 1995; Burnet et al. 1996; Aguirre et al. 1997; Meijer et al. 1997).

It has previously been shown that corticosterone administered once daily at a dose of 5 mg/kg to mice for 10 days leads to a significant attenuation of the 8-OH-DPAT-induced hypothermia (Young et al. 1994). These mice also experience profound adrenal suppression, with corticosterone levels of 15.9 ng/ml compared to 58.3 ng/ml in control animals, at the time of the hypothermia challenge test. This raises the question of whether the effects of repeated administration of

corticosterone lead to an attenuation of somatodendritic 5-HT_{1A} receptor function by means of adrenal suppression. The findings presented here, that ADX does not affect the hypothermic response to 8-OH-DPAT, suggest that this is not the case. It may therefore be the repeated high "pulses" of corticosterone that are responsible for the attenuation, a possibility that is currently under investigation.

The difference in the effect of ADX on somatodendritic as opposed to postsynaptic 5-HT_{1A} receptors may reflect intrinsic differences between these receptors themselves. Alternatively, it may reflect differential modulation of the receptors by corticosteroid receptors. The increase in postsynaptic 5-HT_{1A} receptor mRNA and binding sites in rats after ADX is reversed by corticosterone administration (Mendelson and McEwen 1992; Chalmers et al. 1993; Meijer and de Kloet 1994, 1995; Tejani-Butt and Labow, 1994). Some debate exists concerning whether this effect is mediated by the glucocorticoid (GR) or mineralocorticoid (MR) subtypes of the corticosteroid receptor, since it has been reported that both dexamethasone (Liao et al. 1993; Zhong and Ciaranello, 1995), a GR agonist, and aldosterone (Kuroda et al. 1994), a MR agonist, reverse the effects of ADX on hippocampal 5-HT_{1A} expression. Supporting evidence that the effect is MR mediated comes from findings that the effect of corticosterone is blocked by an MR antagonist (Meijer and de Kloet 1995) and also occur in transgenic mice that are devoid of glucocorticoid receptors (Meijer et al. 1997). If this is the case, then this may explain why the functional activity of somatodendritic 5-HT_{1A} receptors is attenuated by administration of corticosterone acting via GR receptors (Young et al. 1994) but not influenced by ADX, since raphé neurones are known to be devoid of MR receptors (Reul and de Kloet 1985; Harfstrand et al. 1986; Aronsson et al. 1988).

The corticosterone levels found in this study are higher than those previously reported both in rats (Kuroda et al. 1992) and mice (Meijer et al. 1997). The explanation for this difference may partly involve the timing of blood sampling, since corticosteroid levels fluctuate up to 15-fold with the diurnal cycle (de Kloet et al. 1986). However, the more likely explanation is that levels were raised by the prior administration of 8-OH-DPAT. 8-OH-DPAT activates the HPA axis by increasing CRF release (Calogero et al. 1989) and ACTH release (Spinedi and Negro-Vilar 1983), and directly stimulating corticosterone secretion (Calogero et al. 1990). This clearly confounds a possible correlation between corticosterone levels (tested following 8-OH-DPAT administration) and the 8-OH-DPAT hypothermic response. Certainly, the corticosterone levels in the present study are higher than the values determined in this laboratory for ADX mice not given 8-OH-DPAT (data not shown). However, what is clear is that there was a very large difference in the corticosterone levels in ADX versus control and Sham ADX animals (see Fig. 2). This difference is far in excess of the trend towards a difference between sham ADX and control animal corticosterone levels. It can therefore be confidently argued that a substantial reduction in corticosterone levels by means of ADX does not affect 8-OH-DPAT - induced hypothermia in mice.

It is possible that because of the timing of the 8-OH-DPAT hypothermia challenge, 14 days post-ADX, an effect of ADX on somatodendritic 5-HT_{1A} receptor function was not detected. Adaptive processes may have reversed early changes, or alternatively an effect may not have developed by the time the testing was done. However, the effects of ADX on postsynaptic 5-HT_{1A} receptors are seen from 1 hour post - ADX (Zhong and Ciaranello 1995) and very clearly at 14 days (Tejani-Butt and Labow 1994), though by 35 days no difference is seen between control and ADX animals (Tejani-Butt and Labow 1994). The timing of the present study is therefore consistent with previous findings regarding effects of ADX on 5-HT_{1A} receptors. However, performing a hypothermic challenge after a variety of time intervals and with multiple doses of 8-OH-DPAT is required to rule out fully the possibility that ADX affects somatodendritic 5-HT_{1A} receptor function using this model.

We have demonstrated a difference in the modulation of somatodendritic and postsynaptic 5-HT_{1A} receptor function by the HPA axis. It appears that while repeated administration of corticosterone modifies somatodendritic 5-HT_{1A} receptor function (Young et al. 1994), low levels of corticosterone resulting from ADX have no effect. This lack of effect of ADX on somatodendritic, as opposed to postsynaptic, 5-HT_{1A} receptors may be due to the lack of MR expression by raphé neurones (Reul and de Kloet 1985; Harfstrand et al. 1986; Aronsson et al. 1988). In addition, it appears that the attenuation of somatodendritic 5-HT_{1A} receptor following repeated administration of corticosterone (Young et al. 1994) is not as a result of a secondary adrenal suppression given that ADX has no effect. These findings help to further our knowledge of the physiological regulation of central serotonergic function that is likely to be essential for a full understanding of the pathophysiology of human mood disorders.

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