Effects of acute and chronic electroconvulsive shock on noradrenaline release in the rat hippocampus and frontal cortex

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1 Changes in the extracellular content of endogenous noradrenaline (NA) in frontal cortex and hippocampus were determined by *in vivo* microdialysis following acute and chronic electroconvulsive shock (ECS) in rats anaesthetized with chloral hydrate.

2 Basal release of NA in the frontal cortex (4.9 ± 0.3 pg/sample) did not differ significantly from that in the hippocampus (4.6 ± 0.2 pg/sample).

3 A single ECS resulted in an increase of NA release in the hippocampus (21.1 ± 1.3 pg/sample) and in the frontal cortex (11.6 ± 1.2 pg/sample). In both brain regions extracellular NA had returned to basal values within 30 min.

4 Animals were treated chronically with ECS (once per day for seven days). Twenty-four h later (day 8), basal release of NA into dialysis samples from the frontal cortex was significantly increased (50%) as compared to chronic sham controls. Basal release in the hippocampus was not significantly different from the sham controls. In the chronic ECS animals the increase in NA released in both brain areas following an ECS on day 8 did not differ from either the chronic sham controls or from animals given acute ECS.

5 Animals were challenged 24 h after eight ECS or sham control treatments (once per day) with the α_2 -adrenoceptor antagonist, idazoxan (10 mg kg^{-1} , s.c.). Idazoxan increased NA release in the hippocampus in both groups. There was no difference in the magnitude of the response in ECS- and in sham-treated rats. In the frontal cortex, idazoxan increased the extracellular NA content in the chronic sham controls, but the response to idazoxan was significantly attenuated in the chronic ECS animals.

6 Chronic but not acute ECS was found to elicit a sustained (> 24 h) increase in the release of NA in the frontal cortex, but not in the hippocampus. The idazoxan data suggest that the increase may be due to a downregulation of presynaptic α_2 -adrenoceptors in the frontal cortex. The difference in response of these two brain regions to chronic ECS is discussed in terms of differences in the regulation of extracellular NA content by uptake and autoreceptor activation.

Keywords: Electroconvulsive shock (ECS); noradrenaline; frontal cortex; hippocampus; transmitter release; microdialysis; acute ECS; chronic ECS

Introduction

Since Schildkraut (1965) first proposed that depression may result from an underactivity of cerebral noradrenaline-containing neurones, there have been numerous attempts to explain the effects of antidepressant treatments in terms of changes in cerebral noradrenaline (NA) function (see Sugrue, 1981; Green, 1990). Since antidepressant therapies work only after chronic treatment (Oswald *et al.*, 1972; Fink, 1979; Abrams, 1988), most animal studies have focused on the effects of repeated exposure to antidepressants. It is generally agreed that chronic antidepressant therapies produce consistent decreases in the density of β -adrenoceptors in specific brain regions (Kellar *et al.*, 1981; Stanford *et al.*, 1982). ECS has also been shown to decrease β -receptor number (Kellar *et al.*, 1981; Stanford *et al.*, 1982) and function (Przegalinski *et al.*, 1983). The effects of chronic ECS on α -adrenoceptors are less clearly defined, but point to a downregulation of α_2 -receptors (Bergstrom *et al.*, 1979; Stanford *et al.*, 1982). Behavioural data are also consistent with downregulation (Heal *et al.*, 1981; Pilc *et al.*, 1984). The fact that ECS decreases both β - and α_2 -adrenoceptor number and function suggests the possibility that brain NA processes are a common site of antidepressant action.

These changes in adrenoceptor number and sensitivity could result from increases in NA release which occur over time to affect the receptors. Yet studies of brain NA content

or turnover have singularly failed to find any reliable alterations following chronic drug or ECS treatments (see Sugrue, 1981; Green, 1990). Experiments which measure the turnover and/or content of NA suffer in that these measures of NA neuronal activity are indirect and changes in transmitter release can only be inferred. However, the advent of *in vivo* microdialysis has made it possible to monitor directly changes in the extraneuronal content of NA following its release from nerve terminals in specific brain regions.

Two recent reports have used *in vivo* microdialysis to investigate the effects of acute and chronic ECS on the release of endogenous dopamine from the rat corpus striatum (Glue *et al.*, 1990; Zis *et al.*, 1991). Both groups found evidence for increased striatal dopamine release after chronic ECS. Glue *et al.* (1990) also reported that chronic ECS significantly elevated basal NA release in the frontal cortex; while significantly reducing it in the nucleus accumbens. Both groups suggested that enhanced neurotransmitter release could be due to a downregulation of the appropriate presynaptic autoreceptors for dopamine and NA in the specific brain regions.

We have previously shown that the regulation of the extracellular concentration of NA differs between rat frontal cortex and hippocampus (Thomas & Holman, 1991a,b). In frontal cortex, the primary regulation is by activation of the presynaptic α_2 -adrenoceptors; while in hippocampus, NA content in the synaptic cleft is controlled by uptake into the nerve terminal. In the present study the effects of acute and chronic ECS on NA release from rat frontal cortex have been compared with that in the hippocampus. If the effects of ECS

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on NA release are dependent on changes in presynaptic autoreceptor mechanisms then we might expect to see a difference in the response of these two brain regions to chronic ECS. Additionally, to determine whether there are changes in presynaptic α_2 -adrenoceptor function, the effects of the α_2 -antagonist, idazoxan, on NA release were investigated in chronic ECS-treated animals and in chronic sham-treated controls.

Methods

Male Wistar rats (290–320 g) were anaesthetized with chloral hydrate (400 mg kg⁻¹; 100 mg ml⁻¹, i.p.) and supplemented (90 mg kg⁻¹) as required. Animals were placed in the stereotaxic frame and dialysis probes were implanted into either the frontal cortex (AP: +3.2 mm from bregma, L: -1.2 mm, H: -5.3 mm) or hippocampus (AP: -5.8 mm from bregma, LAT: -5 mm; H: -7 mm) using coordinates according to the atlas of Paxinos & Watson (1986). Body temperature was maintained at 37.5°C by use of a rectal probe and heating blanket. The position of each dialysis probe was verified histologically at the conclusion of each experiment. Concentric dialysis probes were constructed as described by Thomas & Holman (1991a). The dialysis probe membrane (4 mm) was polyacrylonitrile (M.W. cutoff 40,000 and supplied by Hospal Medical, New Jersey, U.S.A.).

Each dialysis probe was dialysed with a physiological medium containing (mM): NaCl 147, CaCl₂ 2.3, KCl 4.0 and HEPES 10, final pH 7.4 (Thomas & Holman, 1989) at a flow rate of 2.3 µl min⁻¹ and samples collected every 15 min. At least 1 h passed after implanting the probe before samples were collected. Once sampling commenced, no ECS was administered until basal release was stable and consistent for a minimum of 3 samples. We have previously shown that basal NA release in hippocampus and frontal cortex is neuronal in origin being Ca²⁺-dependent and tetrodotoxin-insensitive (Thomas & Holman, 1991a). Once steady basal NA release was achieved, electrodes were attached to the rats ears and they received a single ECS of 5 s duration and 100 mA intensity (Constant Current Electroshock Unit, Applegarth Electronics, Oxford). Sham control animals were treated in the same way, however, no current was passed through the electrodes attached to their ears. An effective ECS was assessed by the rat undergoing a full tonic/clonic seizure. Dialysis sampling continued for a further 75 min.

In the chronic treatment experiments, separate groups of rats received either ECS (1 s; 100 mA) or sham (1 s; each clipping) treatment once daily for 7 days in the awake state via electrodes applied to their ears. Care was taken to support the rats during the tonic/clonic phase of the seizure in order to prevent injury. On day 8 these rats were dialysed as described for the acute ECS rats.

Two further groups of rats were also treated chronically with either ECS or sham ear clipping to determine whether any functional changes had occurred in the α_2 -adrenoceptors. These were implanted with dialysis probes 24 h after the last treatment and challenged with the α_2 -antagonist, idazoxan (10 mg kg⁻¹, s.c.).

Dialysis samples were analyzed for NA content by high performance liquid chromatography (h.p.l.c.) with electrochemical detection. The mobile phase (sodium acetate 24 mM, citric acid 15 mM, EDTA 3 mM, octane sulphonic acid sodium salt monohydrate 800 µM and 14% (v/v) methanol, pH 5.0) was filtered and degassed before being pumped at a rate of 1 ml min⁻¹ through a Hichrom column (3 µm o.d., 15 cm × 4.6 mm). Electrochemical detection was performed with a Coulochem (ESA, Boston, MA, U.S.A.) with Det 1: +350 mV and Det 2: -350 mV.

Data were analyzed by use of a one-way ANOVA and Dunnett's *t* test. In situations where the variance of the data could not be assumed to be equal a Kruskal-Wallis one-way analysis of variance with a multiple comparison procedure was used.

For the s.c. injection, idazoxan (Reckitt and Colman) was made up in 0.9% (w/v) saline, the concentration of the solutions was such that the rats received the equivalent of 1 mg kg⁻¹.

Results

Effects of acute electroconvulsive shock on noradrenaline release

In the hippocampus, mean ($\pm$ s.e.mean) basal release of NA in the acute ECS- and in the sham-treated animals was 4.5 $\pm$ 0.2 pg/sample (*n* = 5) and 4.9 $\pm$ 0.3 pg/sample (*n* = 5) respectively (Figure 1a). There were no significant differences in basal release between the two groups. ECS administered at the end of the third basal sample resulted in a significant increase in the concentration of NA in the next sample (21.1 $\pm$ 1.3 pg/sample, *n* = 5) (*P* < 0.01). The increased release of NA returned to basal values within 30 min of the stimulus. Animals receiving sham treatment did not have a significant increase in the release of the NA as compared with baseline.

In the frontal cortex, mean basal release in the acute ECS- and in the sham-treated animals did not differ, being 4.1 $\pm$ 0.3 pg/sample (*n* = 4) and 4.5 $\pm$ 0.2 pg/sample (*n* = 4) respectively (Figure 1b). ECS produced a threefold increase in the concentration of NA in the next sample (11.6 $\pm$ 1.2 pg/sample, *n* = 4) which was significantly (*P* < 0.01) greater than basal release. As in the hippocampus, NA release in the ECS-treated animals returned to baseline values within 30 min of the stimulus. Sham treatment alone did not elicit a significant change in NA release.

Figure 1 Effects of acute electroconvulsive shock (100 mA, 5 s; hatched columns) and acute sham treatment (5 s, stippled columns) on noradrenaline (NA) release in (a) hippocampus and (b) frontal cortex. Electroconvulsive shock or sham treatment administered at time zero as indicated by arrow. All values are means with s.e.mean shown by vertical bars (*n* = 4–5). Statistical analysis by ANOVA and Dunnett's *t* test. ***P* < 0.01 versus respective basal release.

Effects of chronic electroconvulsive shock on noradrenaline release

Figure 2a shows that basal NA release in the hippocampus was not significantly different after chronic ECS (4.7 ± 0.4 pg/sample, $n = 6$) as compared with chronic sham treatment (4.3 ± 0.5 pg/sample, $n = 4$). In the chronic ECS group, a further ECS produced a significant fivefold increase in the release of NA above basal levels (20.4 ± 3.8 pg/sample, $n = 5$) ($P < 0.01$). However, this was not significantly different from the ECS-induced release of NA in animals given only a single shock.

In the frontal cortex (Figure 2b), basal release of NA after chronic ECS (6.9 ± 0.9 pg/sample, $n = 4$) was significantly ($P < 0.05$) elevated as compared with the chronic sham treatment (4.6 ± 0.2 pg/sample, $n = 4$) animals. Chronic sham treatment did not alter NA release as compared to the acute sham treatment group. There was a significant ($P < 0.01$) increase in NA release above the basal concentrations immediately after the ECS on day 8 (12.7 ± 2.0 pg/sample, $n = 4$). In order to compare ECS-induced release in acutely treated animals (day 1) and day 8, the respective mean basal release for each experiment was subtracted from the 15 min sample following ECS. A comparison of the NA release in this 15 min sample from animals given either one shock or eight shocks showed there was no significant difference in the response to ECS (day 1: 7.6 ± 1.0 pg/sample, $n = 4$; day 8: 5.8 ± 1.0 pg/sample, $n = 4$).

Figure 2 Effects of chronic electroconvulsive shock once daily for 7 days, 100 mA for 1 s (hatched columns) and chronic sham treatment once daily for 7 days, sham treatment for 1 s (stippled columns) on noradrenaline (NA) release in (a) hippocampus and (b) frontal cortex. Electroconvulsive shock or sham administered at time zero indicated by arrow on day 8. All values are means with s.e.mean shown by vertical bars ($n = 4-6$, hippocampus; $n = 4$, frontal cortex). Statistical analysis by two-way ANOVA with Tukey's multiple comparison test, †† $P < 0.01$ and † $P < 0.05$ for comparison of basal release after chronic ECS or sham treatment. ** $P < 0.05$ comparing stimulated release with respective basal release by one-way ANOVA with Dunnett's t test.

Effects of chronic electroconvulsive shock on α_2 -adrenoceptors function

Basal hippocampus NA release in groups of rats measured 24 h after either eight ECS treatments (3.2 ± 0.3 pg/sample, $n = 5$) or eight sham treatments (3.0 ± 0.2 pg/sample, $n = 5$) was not significantly different with respect to time or treatment group (Figure 3). After a challenge dose of idazoxan, NA release in both the chronic ECS and chronic sham-treated animals was increased, but there was no significant difference between the responses of the two groups. Furthermore, the time course and the magnitude of increased extracellular NA content in the hippocampus following idazoxan in these two groups was similar to that of naive animals challenged acutely with idazoxan (Thomas & Holman, 1991a).

In the frontal cortex (Figure 4), basal release of NA 24 h after the last ECS treatment (5.5 ± 0.1 pg/sample, $n = 5$) was again significantly ($P < 0.01$) elevated in comparison with chronic sham treatment (3.5 ± 0.2 pg/sample, $n = 5$). After a challenge dose of idazoxan to the chronic sham animals (Figure 4a), NA release increased ($P < 0.01$) in a similar manner to acutely challenged animals (Thomas & Holman, 1991b). However, following eight ECS treatments there was no significant increase in NA release in response to idazoxan administration (Figure 4b).

Discussion

We have previously shown that in this anaesthetized rat preparation, the content of endogenous NA present in micro-

Figure 3 Effects of a challenge dose of idazoxan (10 mg kg^{-1}) on noradrenaline (NA) release in the rat hippocampus 24 h after the last of 8 days of chronic electroconvulsive shock or chronic sham treatment. (a) Chronic sham treatment and (b) chronic electroconvulsive shock treatment. Challenge dose of idazoxan administered at time zero as indicated by arrow. All values are means with s.e.mean shown by vertical bars ($n = 5$). Statistical analysis by two-way ANOVA showed no significant differences between the two treatment groups. One-way ANOVA with Dunnett's t test used for comparison of idazoxan challenge dose with respective basal values, ** $P < 0.01$.

Figure 4 Effects of challenge dose of idazoxan (10 mg kg^{-1}) on noradrenaline (NA) release in the rat frontal cortex 24 h after the last of 8 days of chronic electroconvulsive shock or chronic sham treatment. (a) Chronic sham treatment and (b) chronic electroconvulsive shock treatment. Challenge dose of idazoxan administered at time zero as indicated by arrow. All values are means with s.e.mean indicated by vertical bars ($n=5$). Statistical analysis by two-way ANOVA showed significant differences between the basal release of the two treatment groups, $\dagger\dagger P < 0.01$. One-way ANOVA with Dunnett's t test used for comparison of idazoxan challenge dose with respective basal values, $**P < 0.01$.

dialysis samples from both the hippocampus and the frontal cortex is Ca^{2+} -dependent and tetrodotoxin-sensitive. Thus the NA appears to be released from neurones in these brain areas in response to normal nervous activity. Further, the basal concentrations of NA and the responses to idazoxan reported here are in agreement with our own and previous reports (L'Heureux *et al.*, 1986; Dennis *et al.*, 1987; Abercrombie *et al.*, 1988; Thomas & Holman, 1991a,b).

Despite the similarity of baseline NA release, the NA responses to acute and chronic ECS in the frontal cortex and the hippocampus are very different. A single shock administered to animals that have had no pretreatment elicited short term increases in NA release in both brain regions. Glue *et al.* (1990) reported similar results in frontal cortex. Comparison of the magnitude of the NA release in the two regions shows that the response was greater in the hippocampus (fivefold over basal) versus the frontal cortex (threefold over basal). Since ECS will release transmitters by depolarizing nerve terminals, the difference in the amounts of NA released in the two regions may be affected by: (1) differences in the flow of current, (2) changes in neuronal activity caused by the seizures, (3) the greater tissue concentration of NA in the hippocampus versus the cortex (Holman *et al.*, 1976), or (4) the relative involvement of uptake and presynaptic inhibition in regulating extracellular NA levels. We have previously compared dose-response curves to uptake inhibition (desmethylinipramine, DMI, via the probe), α_2 -adrenoceptor inhibition (idazoxan) and to IDX (1.0 mg kg^{-1}) in the presence of increasing concentrations of DMI (via the probe)

on extracellular NA content in the hippocampus and in the frontal cortex (Thomas & Holman, 1991b). From these results we have concluded that the synaptic content of NA in the hippocampus is regulated primarily by neuronal uptake; whilst in the frontal cortex, NA activation of presynaptic α_2 -adrenoceptors is more important. Thus the release of the transmitter in the frontal cortex would favour activation of the inhibitory feedback mechanism to reduce further release. Whereas in hippocampus released NA is normally taken up into the neurone before it can activate the presynaptic feedback mechanism.

A comparison of the response to the ECS stimulus in acute and chronic animals shows there were no differences in either brain region. This suggests that NA transmission does not adapt or become tolerant to the shocks over the course of the treatment. These results agree with a previous report on the frontal cortex (Glue *et al.*, 1990). Interestingly, increases in striatal dopamine release immediately after the last of a series of chronic ECS are attenuated as compared with a single ECS (Zis *et al.*, 1991). Taken together the data emphasise that different transmitters in different brain regions respond differently to chronic ECS.

The most striking result in the present study was the 50% increase in basal NA release in the frontal cortex following chronic ECS which contrasts with the lack of any change in the hippocampus. Glue *et al.* (1990) reported a comparable increase in NA release in frontal cortex. This change in release was only seen after multiple ECS treatment suggesting a similarity with the requirements for therapeutic effectiveness in man. In addition, the change was present for at least 24 h suggesting some sort of long term adaptation to the chronic treatment.

One explanation for the increase in NA after chronic ECS comes from studies in brain slices in which the synthesis and utilisation of NA has been shown to be increased (Kety, 1967; Modigh *et al.*, 1976). This effect also lasted 24 h beyond the last treatment. However, the result has not been replicated by Nimgaonkar *et al.* (1986). A more plausible explanation is suggested by our results with the idazoxan challenges. These data suggests that after chronic ECS the presynaptic α_2 -adrenoceptors in the frontal cortex, but not the hippocampus, are downregulated. Thus the increased basal release of NA would be the result of decreased presynaptic negative feedback due to a downregulation or reduced density of α_2 -adrenoceptors. This conclusion is in agreement with previous binding studies (Stanford *et al.*, 1982) and behavioural observations (Heal *et al.*, 1981; Pilc *et al.*, 1984).

Interestingly, chronic ECS has also been shown to increase NA uptake (Hendley *et al.*, 1974; Minchin *et al.*, 1983; Gleiter & Nutt, 1988) which might be expected to counteract the increase in release and the decrease in presynaptic inhibition. In frontal cortex, uptake has only a secondary role in regulating the extracellular content of NA (Thomas & Holman, 1991b) such that any increase may be masked by the changes in the α_2 -adrenoceptors. On the other hand, in the hippocampus where uptake plays the major role in the control of extracellular NA, any increase in uptake would serve to prevent changes in presynaptic α_2 -receptor function. Further, since the density of α_2 -adrenoceptors is much less in the hippocampus than in the cortex (Hudson *et al.*, 1990), any downregulation of these receptors in the hippocampus would be obscured by neuronal uptake and thus would have less of an effect to increase NA release. The similarity of the response to idazoxan in both the chronic and acute ECS and sham groups in this study is consistent with no downregulation of these adrenoceptors in the hippocampus.

In conclusion, our results demonstrate that chronic but not acute ECS increases NA release in the frontal cortex but not in the hippocampus. The increase in basal NA release and the reduced idazoxan sensitivity in the frontal cortex suggests these effects are mediated by downregulation of presynaptic α_2 -adrenoceptors. It is tempting to speculate that the increase

in basal NA release in the frontal cortex after chronic ECS may contribute both to the reported decrease in β -adrenoceptors found in this region and to the therapeutic efficacy of

ECS. However, such a conclusion must await comparison with the neurochemical effects of other known antidepressant medications.

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