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Subsensitivity of Catecholaminergic Neurons to Direct Acting Agonists After Single or Repeated Electroconvulsive Shock

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Spontaneous firing rates and changes in firing rate in response to an intravenously administered dose of apomorphine were measured after various electroconvulsive shock (ECS) treatment regimens from dopaminergic cells of the substantia nigra in urethane-anesthetized rats. Similar measurements were obtained from noradrenergic neurons of the locus coeruleus before and after intravenous injection of clonidine. A significant decrement in the inhibition of spontaneous firing in response to intravenous administration of these agonists was observed following multiple or single ECS treatment in both substantia nigra and locus coeruleus cells. There was a consistent but nonsignificant tendency for cells in both areas of the brain from treated animals to display higher rates of spontaneous firing than their respective sham-shocked controls. Both the effects on base-line rates of spontaneous activity and on the depression of firing rate in response to drug administration were found to be independent of repeated treatment. A signifi-

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cant negative correlation was obtained between base-line firing rate and percentage depression to the autoreceptor agonist, but this correlation alone was insuffient to account for the observed differences in the drug response. These results are discussed with respect to possible mechanisms of action of electroconvulsive therapy in the treatment of depression.

INTRODUCTION

Although electroconvulsive therapy (ECT) remains an effective treatment modality for severe depression (Avery and Winokur, 1977; Fink, 1978; Scovern and Kilman, 1980), the means by which therapeutic gain is achieved remain unclear. Many authors have established that ECT appears to facilitate monoaminergic neurotransmission in the CNS, an effect which it shares with antidepressant drug administration (Modigh, 1976). These effects are consistent with a theoretical framework emphasizing the role of monoamines, especially the catecholamines, in depression (Schildkraut, 1965; Schildkraut and Kety, 1967). There are data available to suggest that ECT influences catecholaminergic neurotransmission by both presynaptic and postsynaptic mechanisms. For example, in experimental animals, electroconvulsive shock (ECS) appears to increase the turnover of norepinephrine in the brain (Kety *et al.*, 1967) and the activity of tyrosine hydroxylase (Musaccio *et al.*, 1969), as well as inhibit the neuronal uptake of norepinephrine (Modigh, 1976). However, ECS has also been reported to decrease the density of β-adrenergic binding sites in cerebral cortex (Pandey *et al.*, 1979) and the responsivity of adenylate cyclase to norepinephrine (Vetulani and Sulser, 1975; Sulser, 1979). Attempts to demonstrate alterations in α-adrenergic, dopaminergic, or serotonergic receptor binding or turnover of dopamine or serotonin following ECS have been largely unsuccessful (Modigh, 1976; Bergstrom and Kellar, 1979; Kellar *et al.*, 1981).

The spontaneous firing rate of dopaminergic neurons is inhibited by the systemic administration of apomorphine, a direct-acting dopamine agonist (Aghajanian and Bunney, 1973). At low doses, this effect has been suggested to be mediated via presynaptic autoreceptors located on the soma-dendritic regions of these neurons (Skirboll *et al.*, 1979). Recently both behavioral and neurophysiological evidence has been developed which suggests that antidepressant drug administration as well as ECS result in a decreased sensitivity of dopaminergic neurons to apomorphine (Chiodo and Antelman, 1980a, 1980b; Antelman and Chiodo, in press; Serra *et al.*, 1979). Interestingly, Chiodo and Antelman (1980b) observed that this decreased sensitivity of dopaminergic neurons to intravenous administration of apomorhine occurred whether the experimental animals received daily ECS for 6 days followed by a shock-free period of 2 days, or a single ECS followed by a shock-free period of 7 days. A single ECS given 1 hr before assessing the sensitivity of dopaminergic neurons to apomorphine, however, was not effective at inducing the decrease in presynaptic receptor sensitivity.

Recent evidence suggests that dopaminergic neurons possess receptors for their own transmitter both at the level of the presynaptic ending (Farnebo and Hamberger, 1971; Kehr *et al.*, 1972; Starke *et al.*, 1977), and the cell bodies or dendrites (Aghajanian and Bunney, 1973; Groves *et al.*, 1975), and that activation of these autoreceptors reduces dopamine biosynthesis, release, and neuronal activity (Walters and Roth, 1976; Hertting *et al.*, 1978; Groves *et al.*, 1975; Cheramy *et al.*, 1981). A subsensitivity of dopamine autoreceptors would be expected therefore to lead to an increased efficacy of dopaminergic neurotransmission, and this effect might be significant in the antidepressant actions of these treatments (Chiodo and Antelman, 1980b).

The experiments reported here represent an attempt to confirm the single and repeated ECS-induced decreased sensitivity of dopaminergic neurons reported by Chiodo and Antelman (1980b). Further, we have attempted to establish whether this effect is specific to dopaminergic neurons, or represents a more general adaptive response of the CNS to ECS.

METHODS

Experiments were carried out on 71 male Sprague-Dawley rats weighing between 235 and 425 g on the day of recording. Animals were housed two to a cage and allowed ad lib. access to Wayne Lab-Blox F-4 and tap water, and were maintained on a 12-hr light-dark cycle. For investigations of the effects of ECS on autoreceptors on dopaminergic neurons located in the pars compacta of the substantia nigra, rats were first randomly assigned to one of three groups: Control, Single shock, or Multiple shock. Animals in the Single shock group were affixed with ear clips through which a single ECS (60 mA, 700-msec duration, 60 Hz) was delivered. Animals in the Multiple shock group were administered a single ECS with the same parameters once daily for 6 consecutive days, and animals from the Control group were affixed with ear clips once daily for 6 days, but no current was delivered. Following the ECS or sham ECS procedures, animals were returned to individual cages. Electrophysiological determination of autoreceptor sensitivity was performed on the 8 day, that is, 2 days after the final treatment in the case of the Multiple shock animals and 7 days after treatment in the case of the Single shock animals. An additional group, Single shock 1 was included, consisting of animals that had been administered a single ECS with the parameters described above, in which autoreceptor sensitivity was ascertained in substantia nigra 24 hr following this single treatment.

In order to determine if the effects of ECS were limited to dopaminergic neurons, two additional Control and Single shock groups of rats were included. These groups received a sham ECS or single ECS, respectively, and then were evaluated neurophysiologically 7 days later. For these groups, recordings were made from noradrenergic neurons of the nucleus locus coeruleus and the depression in firing rate in response to intravenous administration of clonidine was measured.

On the day of recording, animals were anesthetized with urethane (1.3 g/kg, ip) and a tracheal intubation was performed for the purpose of subsequent artificial ventilation. The left femoral vein was catheterized for the administration of drugs, and the animals were placed in a stereotaxic apparatus using blunt, atraumatic ear bars (Kopf Instruments) coated with anesthetic ointment (5% Xylocaine). The scalp was reflected and, for the purposes of recording from nigral dopaminergic neurons, a small burr hole was drilled at coordinates 0.5 mm anterior to bregma and 3.4 mm lateral to the midline. A bipolar stimulating electrode consisting of insulated stainless steel wires with exposed tips separated by approximately 0.25 mm was placed into the head of the caudate-putamen at a depth of 3.3-3.8 mm from the cortical surface. Another burr hole was made at coordinates 2.1 mm anterior to lambda and 1.9 mm lateral to the midline for the insertion of microelectrodes into the pars compacta of the substantia nigra.

For locus coeruleus recordings, a small burr hole was drilled at coordinates 2.0 mm anterior to lambda and 0.9 mm from the midline. A bipolar stimulating electrode was placed at depth of 5.9-6.0 mm from the cortical surface for stimulation of the dorsal noradrenergic bundle. A larger hole was drilled at coordinates 2.0 mm posterior to lambda and 1.0 mm lateral to the midline, and the transverse sinus was ligated as previously described (Nakamura *et al.*, 1981) for the insertion of microelectrodes into the locus coeruleus. Following completion of the surgical procedures, animals were immobilized with gallamine triethiodide (50 mg/kg, ip) and respired on a Harvard Apparatus rodent respirator at 75-80 cycle/min. Body temperature was maintained at 37 ± 1 C by a heating pad electronically coupled to a Yellow Springs telethermometer, and the electrocardiogram was monitored continuously on an auxillary oscilloscope throughout the experiments. Experiments were performed on animals in matched groups of three per day: one each from the Single shock, Multiple shock, and Control groups in the case of the substantia nigra, and two per day in the case of the locus coeruleus, on Single shock and one Control. The rats were numerically coded on the morning of the experiment to blind the experimenters to the treatment each had received. In addition, the sequence of animals was varied each day to control for any circadian effects. Rats from the Single shock 1 group were run two or three per day.

Responses of presumed dopaminergic neurons of the pars compacta of the substantia nigra, and noradrenergic neurons of the locus coeruleus, were recorded extracellularly with glass micropipettes filled with 3 M NaCl with *in vitro* impedances at 500 Hz ranging from 5-10 Mohms. Single-unit activity was amplified by a WPI preamplifier (Model #M701), displayed on a Tektronix 565 oscilloscope, and recorded on magnetic tape for subsequent analysis.

Presumed dopaminergic neurons of the pars compacta of the substantia nigra exhibited spontaneous action potentials of unusually long duration (2-5 msec) with a relatively low frequency of firing (1.2 Hz-7.2 Hz), characterized by occasional episodes of bursting activity during which the amplitude of each successive action potential decreased progressively within the burst. The initial segment component of the action potential was often clearly delineated. In addition, approximately 75% of the cells could be activated antidromically from

the ipsilateral caudate-putamen. These antidromic responses to suprathreshold stimuli (2-6 mA, 0.1-1.0 msec in duration) occurred at fixed latencies ranging from 9.0-22.0 msec (mean 14.3 msec), exhibited collisions with spontaneously occurring action potentials, and typically consisted of the initial segment spike only. There were no differences between the electrophysiological characteristics of the presumed dopaminergic neurons that were driven antidromically from the neostriatum and those that did not respond to electrical stimulation of the caudate-putamen. These electrophysiological characteristics are in good agreement with those previously reported for identified dopaminergic neurons of rat substantia nigra (Guyenet and Aghajanian, 1978; Grace and Bunney, 1980).

Stimulation of the dorsal noradrenergic bundle at a rate of 1/sec with a pulse of 0.5-msec duration and currents ranging from 0.10-1.0 mA results in the appearance of a triphasic antidromic field response sharply localized to the locus coeruleus as previously described (Nakamura and Iwama, 1975; Huang and Maas, 1976). Antidromic single-unit responses of locus coeruleus neurons appeared superimposed on the field response and were further characterized by their unusually wide wave form (2-5 msec) and relatively slow rate of spontaneous firing (1.0-6.4/sec), consistent with previous reports (Graham and Aghajanian, 1971; Nakamura, 1977; Nakamura *et al.*, 1981).

When neurons satisfying these criteria were encountered, spontaneous activity was monitored for from 5-20 min. Only cells that exhibited stable predrug firing rates (10% or less variability) were used in this study. When a stable firing rate was maintained for at least 5 min, animals were administered either 4 μg/kg or 8 μg/kg apomorphine HCl, the direct-acting dopamine agonist in the case of substantia nigra recording, or 8 μg/kg clonidine HCl, a direct-acting α-receptor agonist in the case of locus coeruleus recording, via the femoral catheter (drug doses are expressed in terms of the salt). These low doses of apomorphine and clonidine have been demonstrated to exert their effects on neuronal firing rate primarily via presynaptic autoreceptors, due to the differential sensitivities and nature of pre- and postsynaptic catecholamine receptors (Skirboll *et al.*, 1979; Svensson *et al.*, 1975; Cedarbaum and Aghajanian, 1977; Svensson and Usdin, 1978). The percentage depression in firing rate in response to the drug was calculated by dividing the firing rate for a 1-min period beginning 30 sec after the drug injection by the mean firing rate of the last 5 min of base line prior to the drug administration. To avoid complications due to residual drug effects, the effects of drug administration were studied in only one cell per animal.

RESULTS

Substantia Nigra

Base-line levels of spontaneous activity in dopaminergic neurons of the substantia nigra in control animals and in the three experimental groups are il-

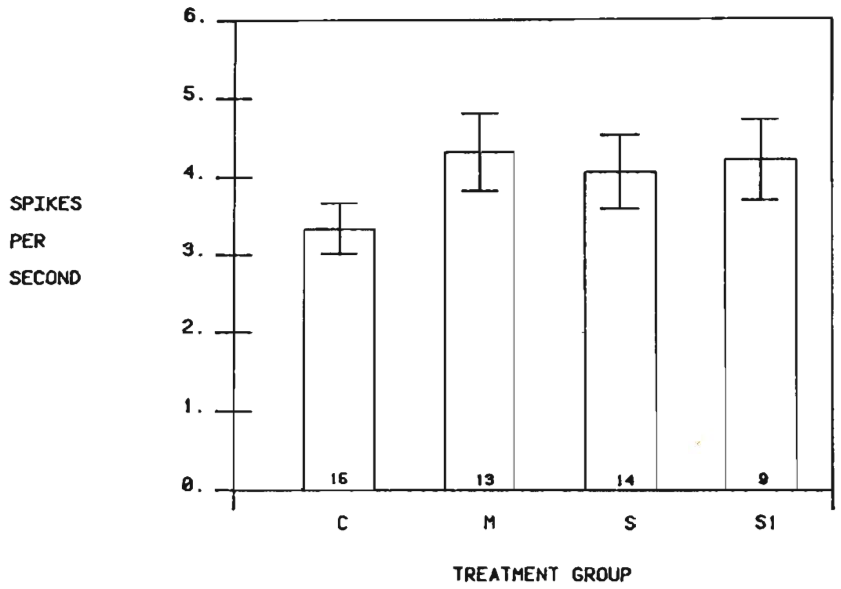

Fig. 1. Spontaneous firing rates of neurons in substantia nigra, pars compacta in Control animals (C), Multiple shock animals (M) that received one ECS per day for 6 consecutive days followed by a 2-day waiting period before recording, Single shock animals (S) that received a single ECS followed by a 7-day waiting period before recording, and Single shock 1 (S1) animals that received a single ECS 1 day before recording. Bar graphs represent the mean ± SEM for five to 20-min periods of base-line spontaneous activity. The numbers inside the bars refer to the number of animals. None of the individual comparisons attained statistical significance.

lustrated in Fig. 1. Although there was a tendency for all the treated animals to exhibit higher firing rates than the controls, analysis of variance revealed no significant main effect of groups on firing rate ($F = 1.10$, df = 3, 47; $p > 0.05$). Newman-Keuls specific comparisons between the control group and each of the experimental groups failed to attain significance ($p > 0.05$).

The mean percentage depression in spontaneous firing rate of substantia nigra dopaminergic neurons following intravenous injection of either 4 μg/kg or 8 μg/kg apomorphine is illustrated for each treatment group in Fig. 2. An analysis of variance revealed significant differences between groups following 4 μg/kg apomorphine ($F = 3.86$, df = 3, 25; $p < 0.05$) and 8 μg/kg apomorphine ($F = 4.24$, df = 2, 16; $p < 0.05$). Specific comparisons using Newman-Keuls tests indicated that the control groups differed significantly from each of the respective shocked groups ($p < 0.05$), while the respective shocked groups did not differ significantly from each other. A significant dose effect was obtained comparing the 8 μg/kg and 4 μg/kg groups over the 4 min following apormorphine ($F = 4.44$, df = 1, 31; $p < 0.05$), which was attributable to the differences between the 4 μg/kg and 8 μg/kg control groups (Newman-Keuls, $p < 0.05$). None of the control animals and only one of the experimental animals (in the 4 μg/kg Multi-

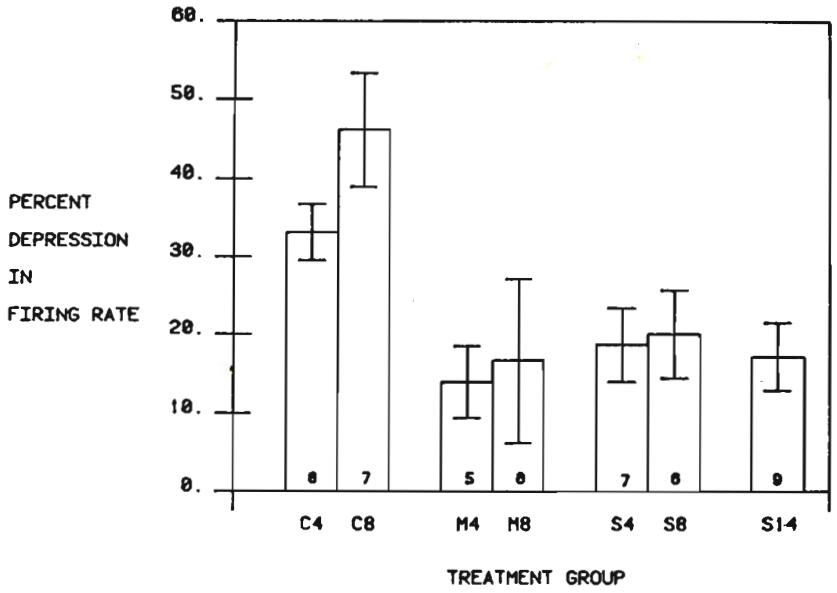

Fig. 2. The mean percentage depression in spontaneous firing rate in neurons of substantia nigra, pars compacta induced by intravenous injection of either 4 or 8 μg/kg apomorphine HC1 as a function of prior ECS treatment. The data are presented as the mean percentage inhibition in the postdrug firing rate relative to a 5-min predrug base line ± SEM. C4, Control animals, 4 μg/kg; C8, Control animals, 8 μg/kg; M4, Multiple shock animals, 4 μg/kg; M8, Multiple shock animals, 8 μg/kg; S4, Single shock 1 animals, 4 μg/kg. The numbers within the bars refer to the number of cells tested, one cell per animal. Each of the shocked groups is significantly different from its respective control group ($p < 0.05$) but no individual comparison between treated groups attained significance. The dose effect is significant ($p < 0.05$) only for the control groups.

ple shock group) responded to the apomorphine injection with a modest increase in firing rate (6.5%).

Locus Coeruleus

The mean base-line rates of spontaneous activity for the Control and Single shock groups are shown in Fig. 3. In a manner congruent with the data from the substantia nigra neurons, there was a tendency for the cells from the treated animals to fire faster than cells from controls, but these differences also failed to attain statistical significance ($F = 1.27$, df = 1, 20; $p > 0.05$).

The mean percentage depression in spontaneous firing rate of locus coeruleus neurons following an intravenous injection of 8 μg/kg clonidine is illustrated for control and shocked animals in Fig. 4. Analysis of variance revealed a significant attenuation of the response to clonidine in the treated animals relative to controls ($F = 9.26$, df = 1, 19; $p < 0.01$). None of the control animals and only one

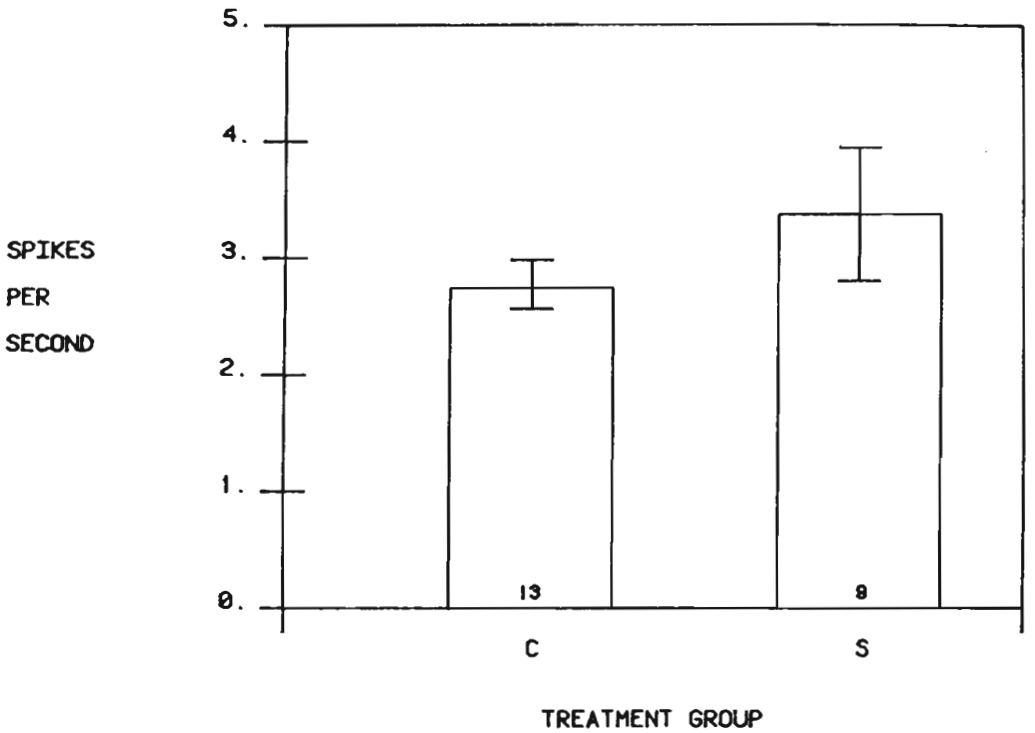

Fig. 3. Spontaneous firing rates of locus coeruleus neurons in Control animals (C) and in Single shock animals (S) that received a single ECS 8 days before recording. Bar graphs represent the mean ± SEM for five to 20-min periods of base-line spontaneous activity. The numbers inside the bar graphs refer to the number of animals. The difference is not significant.

of the experimental animals responded to the clonidine injection with an increase in firing rate (45%).

Inspection of the raw data from both the substantia nigra and locus coeruleus recordings indicated that there appeared to be a relation between the base-line level of spontaneous activity and the magnitude of the depression in firing rate in response to the drug among the control animals. Therefore, all data from control and experimental animals were normalized by a z-transformation and the correlation between the initial spontaneous firing rate and the subsequent percentage depression in response to the drug administration was computed. The resulting negative correlation between base-line firing rate and firing rate depression in response to drug administration ($r = -0.42$, df = 65) proved to be significant ($p < 0.05$). A subsequent analysis of covariance, however, revealed that differences in base-line firing were not sufficient to account for the ECS-induced changes in the responsivity of dopaminergic and noradrenergic neurons to autoreceptor agonists.

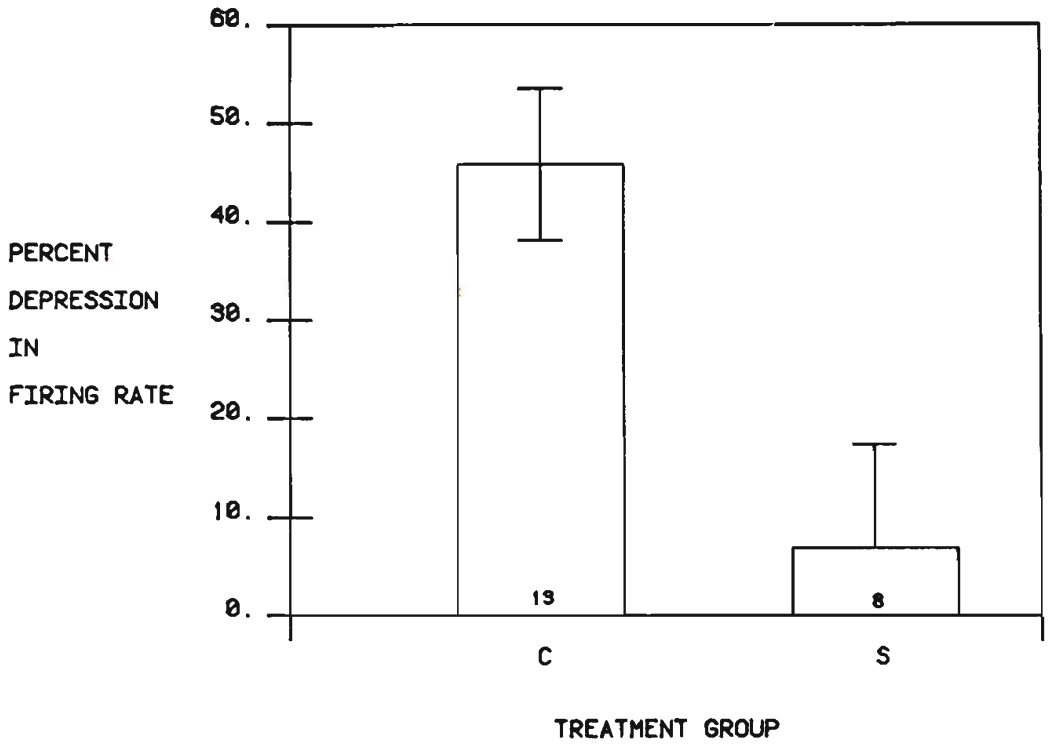

Fig. 4. The mean percentage depression in spontaneous firing rate of locus coeruleus neurons induced by intravenous injection of 8 μg/kg clonidine in Control (C) and Single shock (S) animals. The numbers inside the bar graphs refer to the number of cells tested, one cell per animal. The difference is significant ($p < 0.05$).

DISCUSSION

These studies confirm that ECS can alter the responsivity of nigrostriatal dopaminergic neurons to intravenously administered apomorphine (Chiodo and Antelman, 1980b). In agreement with that report, we found that this effect was independent of the number of treatments. A single ECS followed by a 7-day waiting period before testing was just as effective as 6 daily ECS treatments followed by a 2-day waiting period in reducing the apomorphine-induced inhibition of spontaneous discharge of dopaminergic neurons. We have also found that a single ECS administered just 24 hr prior to testing exerts effects on responsivity to apomorphine that are indistinguishable from those of the other experimental conditions. Thus, whereas no change in the response of dopaminergic neurons to apomorphine was reported 1 hr following a single ECS (Chiodo and Antelman, 1980b), we found that the phenomenon was fully developed 24 hr after a single ECS.

Although Chiodo and Antelman (1980b) obtained an inhibition of approximately 73% following 4 μg/kg apomorphine in their control animals, we obtained a control depression of only 32% to this dose. The reasons for this difference are

not immediately obvious, but may be related to differences in the anesthetic agents used and/or the general level of anesthesia. A depression in firing rate of 32% is consistent with the effects observed at the same dose by others (Skirboll *et al.*, 1979).

The reduction in responsivity of catecholamine neurons to autoreceptor agonists observed following ECS treatments is consistent with the hypothesis that these changes reflect a decrease in the sensitivity of the presynaptic autoreceptor. Chiodo and Antelman (1980a; 1980b) have suggested that such a reduction in autoreceptor sensitivity of dopaminergic neurons following ECS or tricyclic antidepressant drug therapy may be significant in the therapeutic efficacy of these treatments. Although our results indicate that this effect is not specific to dopaminergic neurons, our evidence is still consistent with the view that reduced soma-dendritic presynaptic receptor sensitivity induced by ECS could facilitate catecholaminergic transmission in the CNS. If, for example, spontaneous catecholaminergic neuronal activity were normally inhibited by activation of soma-dendritic autoreceptors, decreased sensitivity of these presynaptic receptors could lead to increased rates of firing in these neurons, thereby facilitating catecholaminergic synaptic transmission (Groves *et al.*, 1975; Cedarbaum and Aghajanian, 1977).

However, in the present study, while all ECS-treated groups exhibited a tendency toward increased mean firing rate, these differences did not reach statistical significance. Furthermore, whereas a single ECT is usually ineffective for alleviation of depression (Fink, 1978), in our hands a single ECS 24 hr before evaluation of dopaminergic autoreceptor sensitivity was as effective as multiple ECS treatments in producing this effect. Thus, it remains to be shown that a reduction in soma-dendritic autoreceptor sensitivity is related to the therapeutic efficacy of ECT.

While catecholaminergic neurons possess receptors for their own transmitters at the level of the cell bodies and/or dendrites, these neurons also appear to have receptors located at the level of their synaptic terminals which act as negative feedback mechanisms controlling biosynthesis or release of catecholamines. Activation of these autoreceptors leads to decreases in biosynthesis and stimulation-induced release of catecholamines, whereas blockade of these autoreceptors results in increased levels of biosynthesis and release (Hertting *et al.*, 1978; Walters and Roth, 1976; Langer, 1974; Starke *et al.*, 1977; Farnebo and Hamberger, 1971). It is conceivable that the alterations in soma-dendritic receptor sensitivity that we have observed here also occur at the level of the terminal autoreceptor and that increased efficacy of catecholaminergic transmission results from this decreased sensitivity. Further research on this question seems justified.

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