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# Effect of Noradrenergic Denervation on Task-Related Visual Evoked Potentials in Rats

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BRENNER, E., M. MIRMIRAN, J. OVERDIJK, M. TIMMERMAN AND M. G. P. FEENSTRA. *Effect of noradrenergic denervation on task-related visual evoked potentials in rats.* BRAIN RES BULL 18(3) 297–302, 1987.—The present study examines whether destruction of the noradrenergic innervation of the forebrain interferes with the processing of sensory information in a manner that results in impaired selective attention. Electro-cortical responses to task-relevant and irrelevant stimuli were found to be sensitive indicators of the rat's attention to the stimuli. The amplitude of the response to the task-relevant stimulus increased as the rat's performance improved. The response to irrelevant flashes of light depended on the predictability of the flashes and on the rat's level of arousal. Noradrenergic denervation (with the selective neurotoxin DSP4) did not affect either the behavioural response to a visual stimulus which the rat had been trained to respond to for a food reward, or the late positive potential evoked by this stimulus. Neither did it affect the response to continuous (temporally predictable) flashes of light that were irrelevant to the task. Although the response to unpredictable flashes was also largely unaffected, we did find an additional late component in this response after DSP4 treatment. These results show that the noradrenergic innervation of the occipital cortex does not always regulate the extent to which visual stimuli are processed, but that noradrenergic neurotransmission may be activated in order to diminish excessive processing of unexpected stimuli.

Noradrenaline Visual evoked potentials Attention DSP4 Operant conditioning Rat

RECENT studies suggest that the noradrenergic fibres innervating the forebrain regulate processes such as selective sensory attention [19, 20, 29], the degree of interaction with diverse environmental stimuli [4–6], and adaptive responses to environmental or physiological challenges [26,27]. The similarity between these suggested processes is that they all address the problem of the extent to which environmental stimuli are processed. However, behavioural studies have repeatedly shown that neurochemical destruction of the noradrenergic innervation of the forebrain does not impair learning of most tasks (reviewed in [20]), and thus—implicitly—that such lesions do not affect processing of the task-relevant stimuli. This led to the suggestion that the dorsal noradrenergic bundle serves to filter out task-irrelevant stimuli [19]. It is widely accepted that the processing of irrelevant stimuli can be blocked at an early stage [14, 15, 21], thus forming the basis for selective attention [9, 14, 15, 18, 21].

One way to measure the extent to which both task-relevant and task-irrelevant stimuli are processed is by recording fluctuations in brain potentials as a result of such stimuli [14, 15, 17]. This procedure is widely used in studies with human subjects. Early components of these sensory evoked potentials have been shown to be influenced by the physical parameters of the stimulus, while late components are known to depend on attentional and motivational factors. The effect of attention on evoked potentials can be demonstrated by asking subjects to attend to certain stimuli. Conspicuous late components that are found when the subject is attending to a stimulus become much smaller or even disappear when the subject is presented with the same stimulus but asked to attend to something else [14,15]. Although one cannot ask animals to attend to certain stimuli, similar late components have been described for rabbits and monkeys that were trained to respond to certain stimuli [1,3]. Furthermore, in rats, late components in the response to continuous flashes of light become smaller with repeated exposure [11], and are proportional to the rat's level of arousal [7,8].

The present study was designed to answer two questions: (1) can specifically attention-related fluctuations in the brain potential be demonstrated in rats: and (2) would destruction of the noradrenergic innervation of the forebrain affect such potentials? In order to answer these questions, we recorded cortical evoked responses to visual stimuli to which the rat had been trained to respond by instrumental conditioning, as well as to task irrelevant visual stimuli that either were or were not temporally predictable. The latter distinction was made because predictable stimuli are easier to ignore than unexpected ones. The noradrenergic innervation of the forebrain was destroyed with the selective neurotoxin DSP4. This compound passes the blood-brain barrier, and can thus

be used to lesion noradrenergic fibres in the brains of adult rats (which already have chronically implanted electrodes) without additional surgery. This enabled us to compare individual rats' responses before and after the lesion, without risking changes in electrode placement.

## METHOD

### *Behaviour*

The present study was carried out in a shielded box (equipped with two levers and a feeder) that was specially designed for recording evoked potentials during operant conditioning. The relevant stimuli were presented via 3 standard green 5 mm light emitting diodes (LEDs) above each of the two levers. Pressing a lever within one second after the LEDs above that lever were (simultaneously) illuminated was rewarded with a food pellet (45 mg dustless precision pellets, Bioserv Inc.). The LEDs were illuminated for 10 msec, giving a light pulse that was just bright enough to be seen. These task-relevant stimuli were presented at random above either of the two levers whenever the rat had not pressed a lever for 4 seconds. The irrelevant stimulus was a bright flash of light (from a Grass PS22 photic stimulator) that was administered through the transparent door of the operant conditioning chamber. This flash was either presented regularly (at a rate of 1 per 2 seconds) or at random (with an average frequency of about 1 per minute).

### *Brain Potentials*

For electrode implantation, rats were anaesthetized with 0.15 ml Hypnorm (fentanyl, Duphar B.V.) and two holes were drilled in the skull, one above the right occipital cortex (3 mm anterior to lambda and 3 mm lateral to the sagittal sinus) and the other above the frontal cortex of the right hemisphere (2 mm anterior to bregma and 1 mm lateral to the sagittal sinus). Stainless steel screws (1 mm diameter) that were driven into these holes were used for extra-dural EEG registrations. These screws were attached to a socket that was fixed to the skull of the rat with cyanoacrylate glue and acrylic dental cement, enabling us to maintain responses to the stimuli for more than two months (over 40 recording sessions) in all rats studied. When recording the brain potentials, the rats were connected to the amplifier via an isolated and shielded 4 lead connector. The wires of the connector, as well as the shielding, were thin and flexible enough to allow the rat to move around freely. Sweeps were discarded whenever the potential before the stimulus fluctuated beyond the range of the AD converter. In differential recordings this was usually only the case when the rat was chewing. In order to reduce movement artefacts, the brain potentials reported in this paper were all recorded differentially. As one would expect on the basis of other studies of visual evoked potentials in rats [7], monopolar recordings from the occipital cortex (with frontal screw connected to ground) showed virtually identical responses to those recorded differentially. The brain potential was amplified (bandpass filtered at 1–1000 Hz) and converted to digital form with a sampling frequency of 1000 Hz. The fluctuations in the brain potential—300 msec before and 500 msec after the stimulus—were averaged separately for the flashes, and for the LEDs stimuli that were followed by the rats pressing the correct lever. A computer programme presented the stimuli and food pellets, and selected and analysed the behavioural and electro-cortical responses.

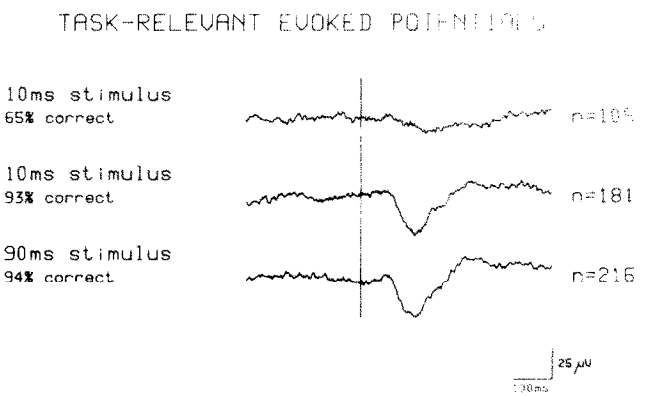


FIG. 1. The electro-cortical response to the task-relevant stimulus depends on the rat's attention to that stimulus, as reflected in its level of performance in the task, but not on the stimulus itself. Data for one rat. The vertical bar indicates stimulus onset. An upward deflection indicates negativity of the occipital lead with respect to that above the frontal cortex. n=the number of responses that were averaged. Note that only sweeps related to a correct behavioural response are included in the average.

Twelve young adult male Brown Norway rats were used in this study. Four of these rats were only used to determine the normal noradrenaline content of the occipital cortex. The other eight were mildly food deprived and trained on the task before implantation of the electrodes and socket. After implanting the electrodes, 7 rats were recorded from for several weeks, until both their behavioural performance and their electro-cortical responses had stabilized. Two rats received continuous flashes of light, whereas the other 5 were subjected to irregular unpredictable flashes. Once we were certain that the brain potentials were sufficiently reproducible, these rats were treated with the selective noradrenergic toxin DSP4 (N-chloroethyl-N-ethyl-2-bromobenzylamine hydrochloride: 50 mg/kg IP [2,12]), and were recorded from for several more weeks. The 8th rat was subjected to both predictable and unpredictable flashes, and was also tested during extinction of the behavioural task in order to examine how the electro-cortical potential responds to various differences in the procedure.

The noradrenaline content of the occipital area was determined by reversed phase high pressure liquid chromatography with electrochemical detection (15 cm Nucleosil 5C18 column; Metrohm 656 detector operated at 700 mV against a Ag/AgCl reference electrode; mobile phase: 0.1 M acetate buffer pH 3.5 with 0.2 mM heptanesulphonic acid delivered at 0.8 ml/min by a Hewlett-Packard 1090 pump. Noradrenaline isolated from homogenates on Sephadex G10.).

## RESULTS

Rats' electro-cortical responses were affected by the attention that they paid to the stimulus, as reflected in the percentage of correct responses that they made during the session. A prominent positive peak was visible in the LED evoked potential when the rats performed almost perfectly. This peak was barely visible when they did not appear to attend to the LEDs, when they performed just above chance level, but increased in amplitude in parallel with the rats' behavioural performance. Increasing the duration of the

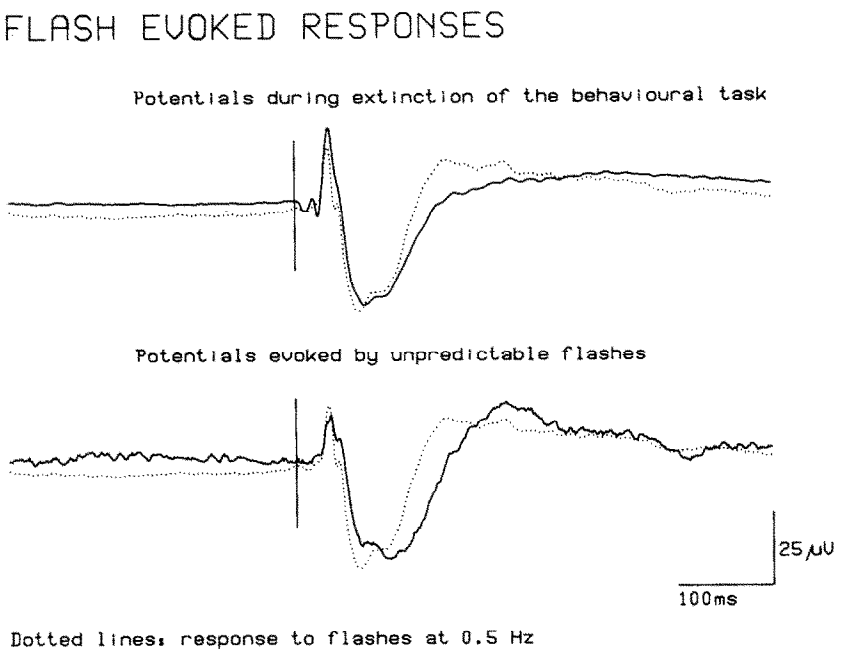


FIG. 2. Responses evoked by continuous flashes of light during performance of a behavioural task (dotted line) and extinction of the task (upper trace); and responses evoked by less frequent unpredictable flashes during task performance (lower trace). Data for one rat. Details as in Fig. 1.

LED stimulus from 10 to 90 msec did not affect the evoked response despite the enhanced visibility of the stimulus (Fig. 1). The response to the task-relevant stimulus was highly reproducible, with peak latencies of about 142 msec (Table 1), varying for each rat within a range of about 25 msec on different days.

The response to the task-relevant stimuli was not affected by increasing the number and predictability of the task-irrelevant flashes. Neither did it change when correct responses were no longer rewarded, although the number of correct responses that were to be averaged decreased very quickly. The rats' responses to the flashes of light were affected by these manipulations in ways that are in good agreement with the sparse literature that is available [7, 8, 11]. The potentials evoked by continuous flashes of light were affected by our stopping to reward the rat for pressing the lever. In that case, the rat stopped pressing the levers, and was observed to sit quietly in a corner of the recording chamber. When the flashes were presented at longer, irregular intervals, they also evoked different responses than when presented in a regular sequence (Fig. 2).

In all rats, DSP4 treatment resulted in substantial depletion of noradrenaline in the areas from which we recorded the brain potentials (Table 1; one rat's tissue sample was lost). Nevertheless, the percentage of lever-presses that were on the correct side was unaffected by this treatment (Table 1). Furthermore, on all but the first few days after treatment, the rats obtained as many rewards per recording session as they had before treatment. DSP4 treatment also had no noticeable effect on the average evoked potentials in response to the task-relevant LED stimuli either for the 5 rats that were subjected to irregular flashes (Fig. 3) or for the 2 rats that were presented with flashes continuously (Fig. 5).

TABLE 1

THE RATS BEHAVIOURAL PERFORMANCE BEFORE AND AFTER DSP4 TREATMENT (PERCENTAGE OF RESPONSES ON THE CORRECT SIDE), THE LATENCY OF THE POSITIVE PEAK IN THE RESPONSE TO THE TASK-RELEVANT LED STIMULUS, AND THE NORADRENALINE CONTENTS OF TISSUE SAMPLES FROM EACH RAT'S RIGHT OCCIPITAL CORTEX

| | Performance (%) | | Latency (msec) | | |
|---|---|---|---|---|---|
| Rat | Before | After | Before | After | Noradrenaline (ng/g) |
| 1 | 96 | 93 | 146 | 147 | * |
| 2 | 89 | 86 | 152 | 141 | * |
| 3 | 83 | 85 | 153 | 142 | — |
| 4 | 83 | 84 | 134 | 155 | 14 |
| 5 | 83 | 82 | 138 | 138 | 34 |
| 6 | 86 | 86 | 145 | 135 | * |
| 7 | 78 | 75 | 144 | 130 | * |
| 8 | 82 | — | 137 | — | 168 |
| 9 | — | — | — | — | 254 |
| 10 | — | — | — | — | 180 |
| 11 | — | — | — | — | 280 |
| 12 | — | — | — | — | 254 |

*Below detection level.

Rats 1 to 5 were subjected to unpredictable flashes, and rats 6 and 7 to continuous flashes. The other 5 rats were not treated with DSP4.

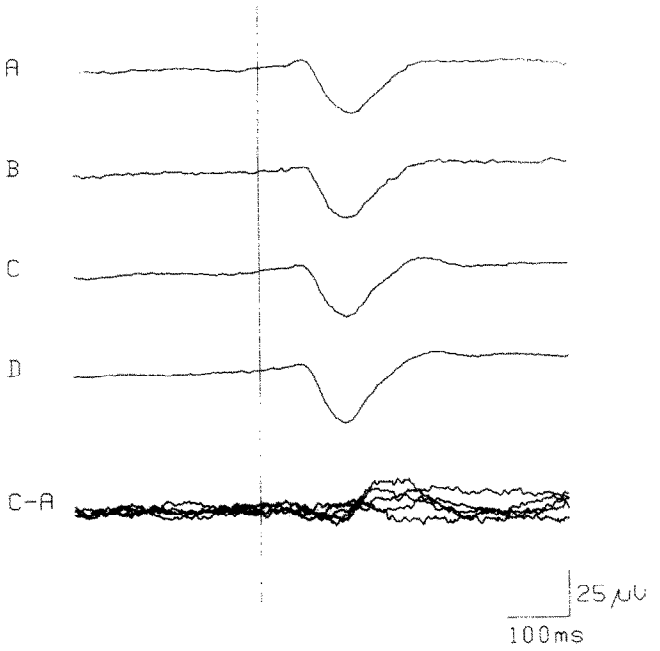


FIG. 3. Effect of DSP4 on the electro-cortical response to the task relevant stimulus. Average of the evoked responses of 5 rats during a 10 day period before DSP4 treatment (A), and on the 1st to 10th (B), 11th to 20th (C), and 21st to 30th (D) day after treatment. In the bottom trace (C–A) the difference between the responses on days 11 to 20 after treatment and those before treatment are shown separately for each of the 5 rats. Other details as in Fig. 1.

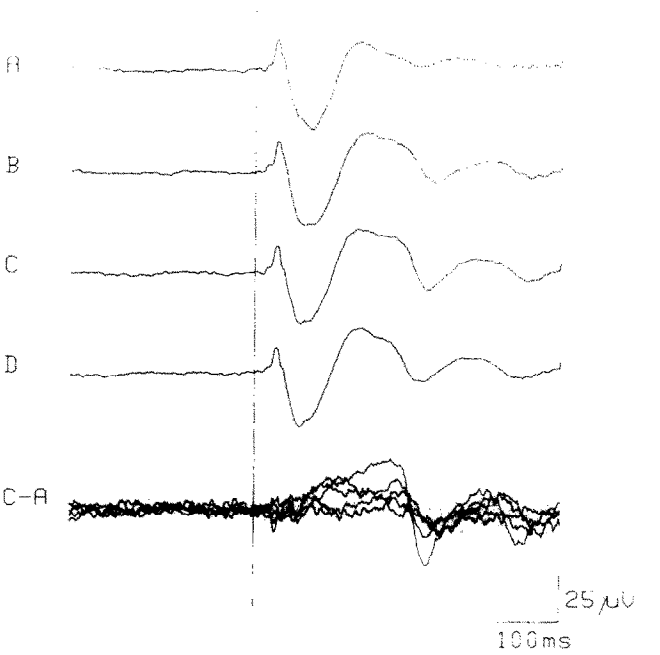


FIG. 4. Effect of DSP4 on the electro-cortical response to an unexpected flash of light. Details as in Fig. 3. Note that the additional peak in the average evoked potentials after DSP4 treatment can be observed in all 5 rats (bottom trace).

There were no consistent differences between individual rats' potentials before and 10 days after noradrenergic denervation with DSP4. Similarly, DSP4 treatment did not have the expected effect on the potentials evoked by temporally unpredictable flashes (Fig. 4): the components that were sensitive to the predictability of the stimulus and to the rats' level of arousal (latencies below 200 msec, also see [7, 8, 11]) were unaffected. However, a component with a peak latency of about 280 msec appeared—or was enhanced—after treatment (bottom trace of Fig. 4). The flash evoked response of the 2 rats that were tested with continuous flashes was unaffected by DSP4 treatment (Fig. 5). Quantification of peak amplitudes confirmed that DSP4 did not affect the amplitude of the positive peak in the response to the task-relevant stimulus or of the large positive peak in the response to the unpredictable flashes. However, it did increase the amplitude of a second positive peak in the response to such flashes. The peak amplitudes in the flash evoked potentials were measured relative to the negative peak between the two positive peaks, and those of the LED evoked potential were measured relative to the prestimulation baseline (Table 2).

## DISCUSSION

In the present study we found highly reproducible responses to the task-relevant stimulus, which appeared as soon as the rats performed above chance level. This response increased with the percentage of correct behavioural responses, but not with stimulus intensity. It appears, therefore, that these evoked potentials can be used as a measure of the extent to which the rats attend to the stimuli. In previous task-oriented evoked potential studies in rats, the rats did not have to respond to the stimuli directly, but the stimuli simply predicted that something would happen after a certain interval [23–25]. Event-related slow potentials were demonstrated in response to an auditory stimulus that either predicted extension of a retractable lever that allowed access to a food reward [24], or preceded rewarding stimulation of the medial forebrain bundle by a fixed time interval [25]. No early components were found in the LED evoked potentials of the present study, but this is not surprising considering the low intensity of the LED stimuli (for effects of various stimuli on early components see [10, 13, 22]).

The potentials evoked by task-irrelevant flashes were affected by the rat's attention to the task, as well as by the schedule of flash presentation. The former confirms previous studies showing that spontaneous changes in behavioural activity affect the electro-cortical response to flashes of light [7]. Changes in flash evoked potentials have been reported in a situation in which behavioural activity was kept as constant as possible by having the rat perform a task while flashes were presented at regular intervals [11]. In that study, the decrease in the amplitude of the late components of the evoked potentials were attributed to habituation to the flashes. In the present study training was continued until no more habituation was observed. Changes in the evoked potentials are interpreted to indicate differences in attentiveness to the flash stimuli.

Drastic depletion of noradrenaline neither influenced the rats' performance nor did it affect the concomitant evoked potentials: there was no change in either the latency or the amplitude of the task-relevant evoked potentials. Irrelevant flashes of light also generally evoked similar fluctuations in

TABLE 2

EFFECT OF DSP4 ON THE AMPLITUDE OF THE RESPONSE TO THE TASK-RELEVANT STIMULUS, AND ON THE AMPLITUDE OF POSITIVE PEAKS WITH LATENCIES OF APPROXIMATELY 90 AND 280 msec IN THE RESPONSE TO UNPREDICTABLE FLASHES

| | Task-Relevant Stimulus | | | | Flash (90 msec) | | | | Flash (280 msec) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rat | Before DSP4 | D1 | D2 | D3 | Before DSP4 | D1 | D2 | D3 | Before DSP4 | D1 | D2 | D3 |
| 1 | 28 | 1.07 | 0.84 | 1.32 | 89 | 1.08 | 1.23 | 1.18 | 52 | 1.38 | 1.81 | 1.77 |
| 2 | 21 | 1.24 | 0.82 | 0.90 | 67 | 0.93 | 0.84 | 0.90 | 33 | 0.86 | 1.17 | 0.97 |
| 3 | 41 | 0.81 | 0.83 | 0.82 | 62 | 0.83 | 1.02 | 0.90 | 19 | 1.12 | 2.13 | 1.48 |
| 4 | 27 | 1.02 | 1.13 | 1.39 | 51 | 0.99 | 1.09 | 0.97 | 12 | 2.03 | 1.76 | 1.38 |
| 5 | 33 | 1.11 | 1.09 | 1.10 | 51 | 1.05 | 0.78 | 0.92 | 18 | 1.33 | 1.46 | 1.16 |
| | | | | | | Mean | | | | | | |
| | | 1.05 | 0.94 | 1.11 | | 0.98 | 0.99 | 0.97 | | 1.34 | 1.67* | 1.35* |

*Significant deviation from 1.00 (2-tailed $t$-test; $p<0.05$).

Amplitude before treatment (in $\mu$V), and the ratio between that on the first (D1), second (D2) and third (D3) ten day period after DSP4 treatment to that before the treatment.

the rats' brain potentials before and after treatment. During the first few days after DSP4 treatment the rats hardly ate, and therefore obviously did not respond to the task-related stimulus. However, a week after DSP4 treatment all rats were pressing the levers in response to the task-relevant stimuli just as often and accurately as they had before treatment. Amphetamine has been shown to depress task related slow potentials in rats performing a task based on the human contingent negative variation paradigm [23,25], and the possibility was raised that this may be due to amphetamine's stimulation of noradrenergic transmission. However, as amphetamine had widespread effects on the rats' behaviour, its effect on the brain potentials may be very indirect [23,25]. The present study shows that some task-related evoked potentials are unaffected by almost total noradrenergic denervation. It is clear from this study that noradrenergic innervation is not under all conditions an important factor in regulating the extent to which visual stimuli are processed within the brain.

DSP4 treatment enhanced a "very late" component in the response to unpredictable flashes of light in all five rats (positive peaks at about 280 msec, see Fig. 4 and Table 2). This was not the case for predictable flashes (Fig. 5). It is unlikely that this change is simply due to time or to experience with the stimuli, because the rats had received ample experience before treatment in order to make sure that their evoked potentials had stabilized. No such change was found in other peaks of the response to the unexpected flashes, or in the responses to the continuous flashes or the task-relevant LEDs stimuli. The late positive component in the potential evoked by the unexpected flashes after DSP4 treatment suggests that unexpected stimuli influence the brain more extensively when the noradrenergic innervation is destroyed. Cells in the noradrenergic locus coeruleus have been shown to respond to novel neutral stimuli, but to stop responding to these stimuli upon repeated presentation, even when the stimuli are associated with food reward [16, 27, 28]. In the present study, the more prominent late component in the evoked response to unpredictable flashes (in comparison with that to continuous flashes; Fig. 2) suggests that unpredictable flashes maintain some novel/arousing properties. Noradrenergic cells may be activated by unexpected (or noxious) stimuli [16,26] in order to inhibit over-reaction to stimuli with which the animal has not yet learned to cope. Such a mechanism would leave potentials evoked by predictable task-relevant or irrelevant stimuli unaffected after norad-

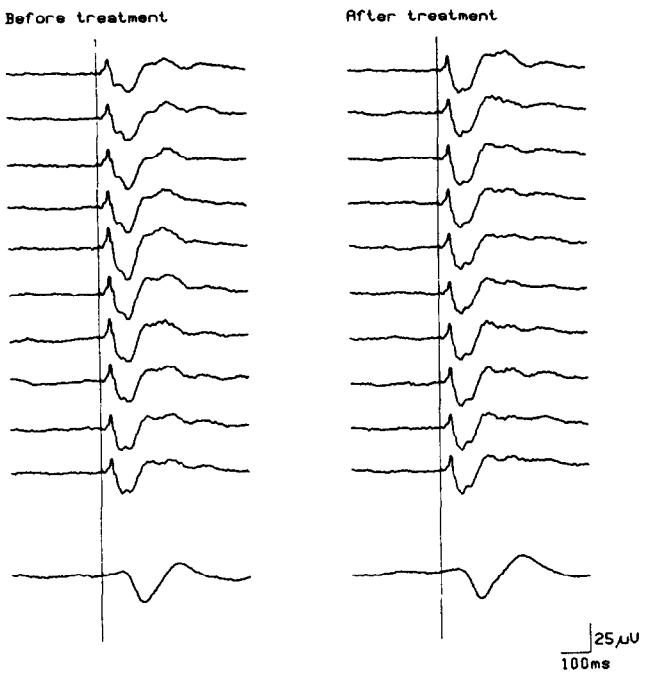


FIG. 5. Average of 2 rats' mean electro-cortical responses to regular (once every 2 seconds) flashes of light on 10 days before and 10 days after DSP4 treatment (allowing 10 days for recovery). The bottom traces show the average responses to the task-relevant stimuli before and after treatment.

renergic lesions, and at the same time could account for the additional late peak in the response to "unexpected" stimuli after deterioration of such inhibition. Over-reacting to novel situations may account for some of the effects of noradrenergic lesions on "attention." We conclude that the noradrenergic innervation of the occipital cortex does not always regulate the extent to which visual stimuli are processed, but that it may inhibit excessive "late" responses to unexpected stimuli.

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