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Mediation of Footshock Sensitivity by Serotonergic Projection to Hippocampus[1]

ROBERT F. SMITH

Department of Psychology, George Mason University, 4400 University Drive, Fairfax, VA 22030

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SMITH, R. F. *Mediation of footshock sensitivity by serotonergic projection to hippocampus.* PHARMAC. BIOCHEM. BEHAV. **10**(3) 381–388, 1979.—The present experiments assessed the effects of changes in serotonergic function on footshock sensitivity, as determined by a quantified version of the flinch-jump assessment method. In Experiment 1, depletion of telencephalic serotonin by PCPA injection, medial forebrain bundle lesion, or septal lesion, produced increases in reactivity which were correlated with reductions in telencephalic serotonin levels. In all cases, this increased sensitivity was reversed by injections of d,l-5-hydroxytryptophan (5-HTP) which restored telencephalic serotonin levels to normal. This effect of 5-HTP had not previously been demonstrated in septal lesioned animals, and overall levels of reactivity of septal animals to other stimuli were also reduced by 5-HTP. Experiment 2 tested the effects of hippocampal lesion on the 5-HTP effect in animals with serotonin depletion produced by either PCPA or septal lesion. Hippocampal lesion, while not increasing footshock sensitivity further, significantly attenuated the effectiveness of 5-HTP in restoring sensitivity to normal. The results suggest that hippocampus may be an important site of action of serotonin in modulating reactivity to footshock, and that failure of raphe lesions to increase reactivity may be due to failure to adequately deplete hippocampal serotonin.

Footshock sensitivity Hippocampus Septal area Serotonin

THE KNOWN serotonin-containing perikarya of the central nervous system are largely contained within the several raphe nuclei of the mesencephalon, with axonal projections to telencephalon, diencephalon, and spinal cord [31]. Tenen [30] reported that the serotonergic system may be involved in sensitivity to footshock. Depletion of serotonin by p-chlorophenylalanine (PCPA) increased sensitivity to footshock, and this increase was reversed by d,l-5-hydroxytryptophan (5-HTP)-induced repletion of serotonin. Other manipulations of whole body serotonin, such as diurnal variations [24], and feeding a corn diet low in tryptophan [17] are also effective in changing the rat's sensitivity to footshock, with reductions in serotonin correlated with increases in sensitivity to footshock.

Harvey and his colleagues have produced evidence that the serotonergic system involved in the modulation of reactivity to footshock is an ascending system to forebrain. Harvey and Lints [4] demonstrated that lesions of the medial forebrain bundle (MFB) produced increases in sensitivity to footshock which were correlated with depletion of forebrain serotonin produced by the lesion. Lints and Harvey [14] replicated this finding and further showed that increased footshock sensitivity produced by septal lesion was also correlated with the decrease in forebrain serotonin produced by the lesion. In the MFB lesioned preparation, injections of 5-HTP restored footshock sensitivity to normal in a dose-related fashion [15].

A major discrepancy to date has been the failure of lesions of the raphe nuclei to increase footshock sensitivity. Hole and Lorens [8] reported that lesions of the raphe nuclei which substantially lowered forebrain serotonin levels failed to produce detectable changes in footshock sensitivity, and injections of 5,7-dihydroxytryptamine into the MFB, which lower ^{3}H-serotonin uptake in forebrain, similarly have little effect on footshock sensitivity [7]. The findings of the present paper will suggest a resolution to these apparent discrepancies.

The available data, then, suggest that there may be a serotonergic projection to forebrain which is involved in the modulation of reactivity to footshock. While some of the effects of 5-HTP in restoring footshock sensitivity to normal may be due to peripheral actions of serotonin such as have been demonstrated in spinal cord [21], the MFB and septal lesion data indicated that there must also be an important central site of action. However, a specific central site of action has not been identified. While Lints and Harvey [15] interpreted their data on the effects of 5-HTP in the MFB preparation in terms of demonstrating the importance of serotonergic mechanisms, their data also indicate that they did not destroy the site of action of serotonin. If a site of action of serotonin were destroyed, 5-HTP could not restore footshock sensitivity to normal. The present paper will address the question of the location of that site.

Experiment 1 of the present paper was designed to rep-

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licate and extend the previous findings of the effects of serotonin-reducing manipulations on footshock sensitivity, and the effectiveness of 5-HTP in reversing such effects. Previously used manipulations such as MFB lesion, raphe lesion, and PCPA injection were included. In addition, since Harvey and Lints [4] have shown that increased shock sensitivity in the septal preparation is related to serotonin reduction (but have not investigated the effects of repletion via 5-HTP), a septal lesioned group was included in the present investigation. Since septal lesion also depletes hippocampal acetylcholine [22], an additional group given scopolamine was included. Experiment 1 was designed to (1) confirm previous findings of increases in shock sensitivity following serotonin-reducing manipulations, and (2) determine whether 5-HTP restores shock sensitivity to normal in all of the serotonin-reduced groups, especially the septal lesioned group.

EXPERIMENT 1

Animals

Male Sprague-Dawley rats, 275–300 g, were housed in individual cages on a 12:12 light-dark schedule, with ad lib access to food and water.

Surgical Procedures

All animals sustaining standard stereotaxic surgery were pretreated with 0.25 ml atropine sulfate and anesthetized with 45 mg/kg sodium pentobarbital.

Raphe Lesion

A direct approach from above was utilized by exposing the sagital sinus from a lateral approach, and positioning the lesioning electrode adjacent to the sinus (0.2–0.4 mm right lateral). Unilateral lesions were created with 1.0 mA anodal current for 15 sec at –6.3 mm (from bregma) and 7.8 mm below skull to damage the median raphe. The same electrode was then raised to –5.7 mm, and 1.0 mA passed for 8 sec to damage the dorsal raphe.

MFB Lesion

Bilateral destruction was effected by 1.0 mA current for 15 sec at coordinates of –2.0 mm, ± 1.3 mm, –8.7 mm.

Septal Lesion

Bilateral damage was effected by 2.0 mA for 25 sec at coordinates of +1.0 mm, ± 0.5 mm, –5.5 mm.

Chemical Injection Procedures

PCPA. The initial dosage of 300 mg/kg, d,l-parachlorophenylalanine (Regis Chemical Co., Morton Grove, IL), was prepared by the method of Tenen [30] and given intraperitoneally as a suspension in 10 ml/kg volume. Additional maintenance doses of 100 mg/kg were given on alternate days beginning the fourth day following the initial dose. PCPA was begun at least seven days prior to testing, and testing followed a maintenance dose by at least 22 hr. Four days after testing was concluded (48 hr after a maintenance dose, 5 total maintenance doses), the animals were sacrificed for serotonin assay.

Saline (control for PCPA). Normal saline was combined with the same volumes of NaOH and HCl used to prepare the PCPA, to produce a solution of approximately the same pH as the PCPA (2.0). Injection volumes and schedules were identical to those of the animals receiving PCPA.

5-HTP. A dosage of 105 mg/kg d,l-5-hydroxytryptophan (Regis Chemical Co., Morton Grove, IL) was injected intraperitoneally 40 min prior to footshock testing.

Saline (control for 5-HTP). An identical 4 ml volume of normal saline was injected 40 min prior to footshock testing.

Scopolamine. A dosage of 2.0 ml/kg scopolamine hydrobromide in 0.4 ml injection volume was injected 40 min prior to behavioral testing. No injection control group was employed, since the total injection volume for this group was only 10% greater than for other groups receiving only saline or 5-HTP.

Apparatus

A 20×20×7 cm Plexiglas chamber was equipped with a shock grid floor. The Plexiglas was rigidly connected to a telephone diaphragm, producing a voltage output whenever the cage was moved. This voltage produced a pen deflection on an Esterline-Angus recording milliammeter.

For shock delivery, an Automated Data Systems 1248A timer-counter with counter slave controlled a stepping switch, rheostat network, and a BRS/LVE SGS-003 shock generator/scrambler. Shock intensities of 0.2 to 2.0 mA in 0.2 mA increments were delivered in an automatic ascending, then descending pattern.

Design

All animals were tested on shock reactivity under both the 5-HTP and saline drug injection conditions, counterbalanced for order of presentation within groups. Since pilot data indicated residual effects of 5-HTP for up to three days, five days elapsed between testing under 5-HTP and saline conditions.

Procedure

Animals were placed in the Plexiglas chamber and allowed to habituate for 2 min prior to shock sensitivity testing. They were then administered four series of shocks, with ten shocks in ascending order of magnitude and ten in descending order within each series. Fifteen sec elapsed between individual shocks, with 2 min between series. Total test time was 25 min.

Before analysis, animals suffering clear motor deficits were eliminated from data analysis. Group numbers of the animals which survived the surgery without pronounced debilitation were as follows: control—10, saline—7, MFB lesion—4, septal lesion—8, raphe lesion—9, PCPA—10, and scopolamine—9. This discarding produced a bias toward increased reactivity in the raphe and MFB groups.

Data were hand scored, and thresholds for four arbitrarily selected response amplitudes of 5, 10, 20 and 40 mm pen deflection were calculated by interpolation between median responses at each shock intensity. These response amplitudes roughly covered the range between a medium flinch and a large jump.

In addition to footshock sensitivity, it was noticed that the first two squads (one/group) of animals appeared much less reactive overall after 5-HTP than after saline. Consequently, all subsequent squads were tested for general reac-

tivity by the method of Seggie [29]. Group sizes for these animals were: control—8, saline—6, MFB—4, septal lesion—6, raphe lesion—7, PCPA—8, and scopolamine—7.

Serotonin Assay

Five days after completion of behavioral testing, animals were sacrificed by decapitation 40 min after either saline or 5-HTP. The brain was rapidly dissected out, bisected along the longitudinal fissure, and telencephalon was separated from diencephalon under visual guidance. Telencephalon assayed included cortex, hippocampus, striatum, but not olfactory bulbs. After dissection the sample tissues from each hemisphere were immediately pooled, wrapped in aluminum foil, and frozen on dry ice. Elapsed time from sacrifice to placing the tissue on dry ice was 2.5–3.0 min. Tissue samples were stored at −70°C until serotonin estimation, using the assay technique of Maickel, *et al.* [18], including two borate buffer washes to eliminate fluorescence contribution from 5-HTP.

RESULTS

Serotonin Assay

Table 1 indicates the estimated serotonin content obtained from a representative sample of each treatment group after saline injection, and also for each group after receiving 105 mg/kg 5-HTP 40 min prior to sacrifice. As indicated, MFB, PCPA, raphe, and septal animals had significantly reduced telencephalic serotonin, while 5-HTP injections restored all groups to above normal except the septal animals, which remained nonsignificantly lower than controls.

Behavioral Results

An analysis of variance was first conducted on the calculated response thresholds to determine the effects of the various manipulations under the saline condition, i.e., without serotonin repletion (Fig. 1). This analysis revealed significant treatment, $F(6,50)=3.64$, $p<0.01$ and response amplitude, $F(3,150)=83.42$, $p<0.01$, effects. A Newman-Keuls analysis of the groups main effect indicated that the septal lesioned, MFB lesioned, and PCPA groups had significantly lower overall thresholds to footshock than the unoperates and control groups ($ps<0.05$). Scopolamine and saline treated rats failed to differ from controls, and are omitted from the figure for clarity. The repeated measures effect indicated that subjects exhibited a higher threshold for successively more vigorous responses. The interaction effect did not approach significance ($F>1$).

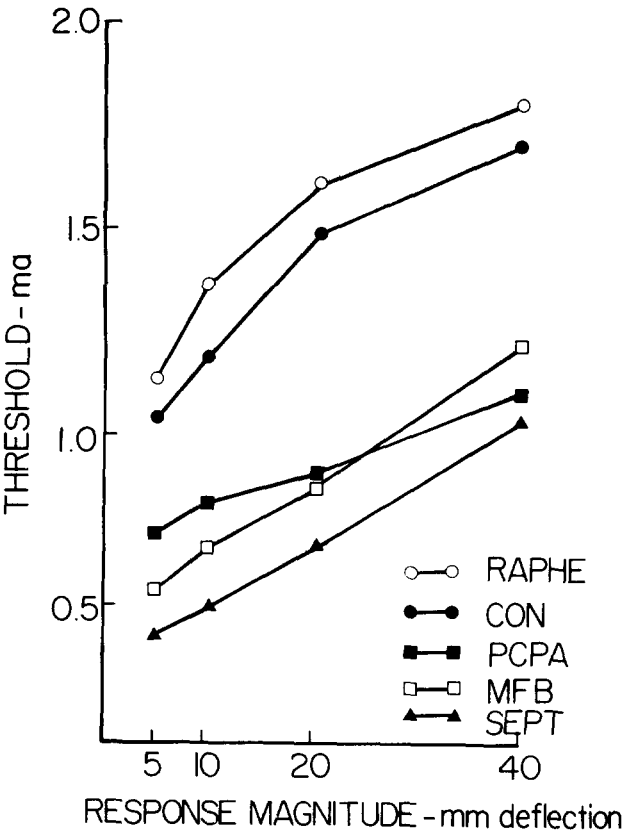

FIG. 1. Mean threshold intensity at each of four successively greater response amplitudes. All groups with depleted serotonin (except raphe lesion) require lower shock intensity to produce any of the four response magnitudes for which thresholds were calculated. Saline and scopolamine groups are omitted for clarity, and did not differ from the controls.

TABLE 1

TELENCEPHALIC SEROTONIN CONTENT (μG/G ± SEM) FROM REPRESENTATIVE ANIMAL OF EACH OF THE TREATMENT GROUPS, WITH AND WITHOUT SEROTONIN REPLETION BY 105 MG/KG 5-HTP. VALUES ARE CORRECTED FOR RECOVERY (56.2%) AND WERE TAKEN FROM ANIMALS SACRIFICED 30 MIN AFTER EITHER SALINE (LEFT) OR 5-HTP (RIGHT). GROUP SIZES ARE IN PARENTHESES.

	Saline		5-HTP	
	Serotonin Content	% Untreated Control	Serotonin Content	% Untreated Control
Control	0.494 ± 0.095 (4)	100.0	0.560 ± 0.188 (4)	113.0
MFB	0.275 (2)	55.8	0.565 (2)	114.4
Raphe	0.343 ± 0.149* (4)	69.6	0.572 ± 0.094 (4)	115.7
Septal	0.334 ± 0.069* (4)	67.6	0.435 ± 0.025 (4)	88.1
PCPA	0.165 ± 0.110* (4)	33.4	0.559 ± 0.054 (4)	113.2
Saline	0.413 ± 0.145 (4)	83.6	0.598 ± 0.027 (4)	121.1

*Significantly different from control-saline ($p<0.05$, t-test).

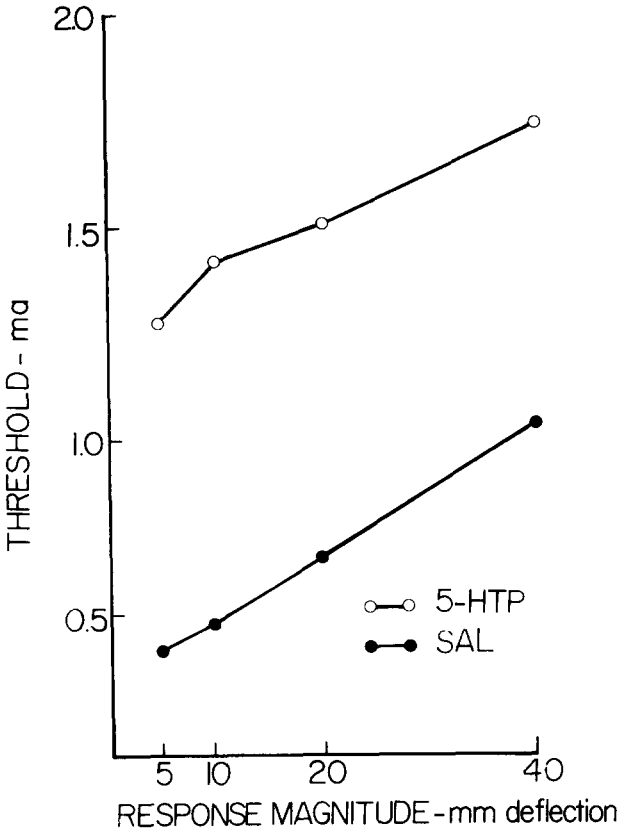

FIG. 2. Mean threshold to each of four response magnitudes in septal lesioned animals, after saline (bottom curve) and 5-HTP (top). Dosage of 5-HTP which restores forebrain serotonin to near normal also elevates shock threshold at each response amplitude to near normal.

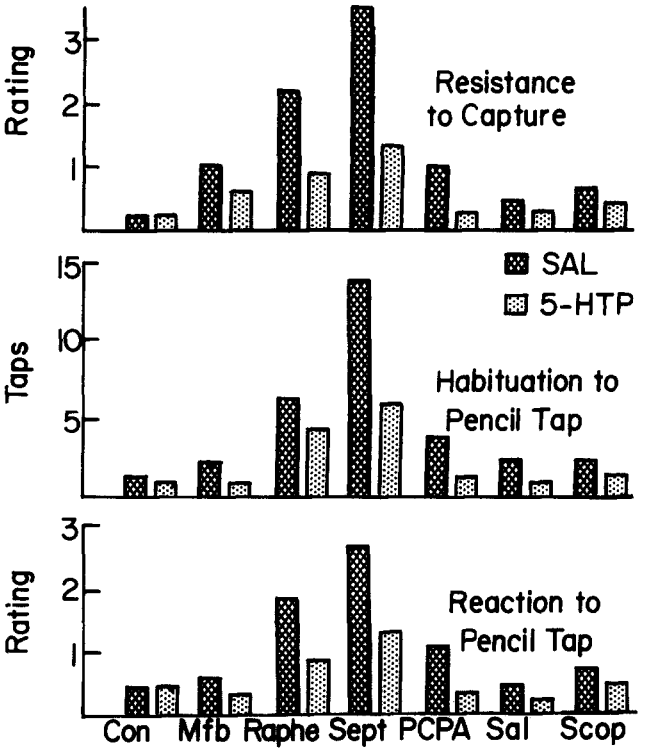

FIG. 3. Emotionality ratings for Experiment 1. Note the relationship between serotonin level and reactivity within each group, especially in the septal lesioned group.

A similar analysis of variance which also included data from each subject after injection of 105 mg/kg 5-HTP indicated a significant treatment effect, $F(1,50)=82.35$, $p<0.01$, indicating that the dosage of 5-HTP employed significantly raised the current level required to produce a given response amplitude. Inspection of the data indicated that this was true of all groups. While this effect of 5-HTP had been previously demonstrated for most groups included in the present study, the data for the septal lesioned group is of special interest. Figure 2 presents this data for the septal group under saline and 5-HTP conditions, and clearly indicates that 5-HTP raises the current threshold for producing a given response amplitude. Further, the magnitude of the 5-HTP effect in septal animals is comparable to that in PCPA animals (not shown), in which presumably no neurons are destroyed. This suggests that septal lesion does not destroy the neurons upon which 5-HTP acts.

Figure 3 presents the data for emotionality ratings for animals in the various treatment groups. An analysis of variance and subsequent Newman-Keuls tests indicated that the septal lesions rats were more reactive than controls on all measures taken ($p<0.01$). The raphe lesioned animals were also more reactive to capture ($p<0.05$). Scores for all groups tended to be lower on all measures after 5-HTP injection, compared to following saline injection. Of particular interest in the septal lesioned group, which showed significant ($p<0.05$) recovery after 5-HTP. The septal lesioned animals remained apparently different from controls, however; while not nearly as reactive as septal lesioned animals after saline injection, they remained visibly tense and slightly more reactive than normal. This apparent difference was not statistically significant ($0.10>p>0.05$).

DISCUSSION

The present experiment confirmed previous findings of Lints and Harvey [14] and of Tenen [30] that animals with serotonin reduction by septal lesion or PCPA are more sensitive to footshock than are animals with normal serotonin concentrations. MFB data, though biased towards increased reactivity, also tended to confirm previous findings of Harvey's group. Further, the present data indicated that animals with septal lesions, as well as PCPA treated and MFB lesioned animals, are significantly affected by 5-HTP injection which return telencephalic serotonin levels to near normal; footshock sensitivity is inversely related to telencephalic serotonin concentration. This finding suggests that the cell bodies which mediate the effects of 5-HTP in lesioned animals do not lie in septal area, since destruction of such cell bodies would reduce effectiveness of 5-HTP in returning footshock sensitivity to normal levels.

Failure of raphe lesions which reduce telencephalic serotonin content by 30% to also increase footshock sensitivity, even after discarding debilitated animals, is consis-

tent with previous results [7], but is difficult to explain. In view of the quantity of data supporting the notion that serotonin levels are inversely related to footshock sensitivity, it would be premature to abandon this notion because of the failure of raphe lesions to increase sensitivity. An alternative explanation is that the functional relationship of serotonin to footshock sensitivity lies in a more restricted area than all of forebrain, and the raphe lesions which have been employed in the past may produce substantial average depletions of forebrain serotonin while sparing a critical area within forebrain. Experiment 2 will address the question of the location of the critical structure.

In addition to adding further support to the notion that a serotonergic projection to telencephalon is involved in the modulation of reactivity to footshock, the present data also indicate that the hyperreactivity syndrome often reported in septal lesioned animals may be importantly related to serotonin depletion produced by the lesion. While 5-HTP failed to restore septal lesioned animals entirely to 'normal' levels of reactivity, there was a marked (and significant) calming effect of 5-HTP. While it is beyond the scope of this paper to argue that there is a serotonergic modulation of reactivity to many forms of stimulation, such an hypothesis might explain a portion of the hyperreactivity observed following septal lesion. The present findings also suggest that 5-HTP injection may separate the hyperreactivity effects of septal lesion from other effects produced by neural damage.

EXPERIMENT 2

The finding that 5-HTP given to animals sustaining septal lesion restores reactivity to normal additionally indicates that the locus of action of the repleted serotonin cannot be in the septal area. The question therefore arises of where serotonin acts to modulate footshock sensitivity. Moore and Halaris [20] have recently demonstrated that there is a substantial serotonergic projection to hippocampus, which reaches hippocampus by two discrete pathways, cingulum and dorsal fornix. In addition, Segal [28] has shown that either stimulation of raphe neurons or iontophoretic injection of serotonin to hippocampal neurons affects the firing of hippocampal neurons, with inhibition of firing as the predominant effect. Since the effects of raphe stimulation on firing rate of hippocampal neurons was nearly abolished by PCPA, the author concluded that there is a serotonergic projection to hippocampus which acts largely to inhibit firing of hippocampal neurons.

Such findings add some anatomical and functional definition to the established knowledge that hippocampus has a relatively high serotonin content in relation to other forebrain structures [25], and allow the possibility that this projection to hippocampus might underlie serotonergic modulation of footshock sensitivity. There are a number of data which indicate that hippocampus may be involved in higher level processing of sensory input and/or motor output. Although hippocampus is no longer regarded as an olfactory structure [23], it does receive input from most, if not all, sensory modalities [13,27], making it a likely structure for modulation of reactivity to stimuli.

Jacobs' group has demonstrated that the hippocampal serotonin content is derived almost exclusively from the median raphe nucleus [11] and that this projection mediates the activity increases found following lesion of the raphe nuclei [10]. The present study, in an effort to assess whether footshock sensitivity increases following serotonin depletion are due to changes in (all or part of) hippocampus, used a modification of Jacobs *et al.*'s [10] procedure of combining hippocampal lesion with a serotonin-reducing manipulation. If hippocampal serotonin content is a determinant of footshock sensitivity, at least three predictions can be made: (1) hippocampal lesion alone might increase sensitivity to footshock; (2) if serotonin reducing manipulations and hippocampal lesion affect footshock sensitivity through a common system, the two types of manipulations may not be additive; and (3) hippocampal lesions must substantially reduce the action of 5-HTP in restoring footshock sensitivity to normal following a serotonin-reducing manipulation—if 5-HTP has normal effectiveness in a hippocampally lesioned animal, then the site of action of 5-HTP must be intact.

METHOD

Animals, Apparatus, and Procedure

Animals, housing apparatus, and procedure were the same as in Experiment 1. Eight animals were included in each of six groups: unoperated, septal lesion, PCPA, hippocampal lesion, septal lesion+hippocampal lesion, PCPA +hippocampal lesion.

Hippocampal lesion. Aspiration techniques were used as described by Isaacson, Douglas, and Moore [9]. Briefly, bilateral bone flaps were removed between lambda and bregma, exposing the neocortex. Using suction connected to a blunted 18 gauge needle, overlying cortex was removed to exposed hippocampus. The suction needle was then used to transect hippocampus at the point of exposure, and ventral and dorsal hippocampus were removed sequentially. An attempt was made to remove as much as possible of hippocampus without substantial damage to thalamus or other subcortical structures.

RESULTS

Histology. Septal lesions at the parameters used in the present study were large and bilaterally symmetrical, and destroyed the medial and lateral septal nuclei. Damage occasionally extended into the nucleus accumbens septi, but damage to caudate-putamen was rare and slight.

Hippocampal lesions were comparable to those of Isaacson, *et al.* [9]. Bilateral hippocampal damage was extensive in all animals, with occasional sparing of the extreme anterior portions of dorsal hippocampus, and frequent sparing of extreme ventral hippocampus. Extent of hippocampal damage was compared with behavioral scores, but were not apparently correlated, nor was extrahippocampal damage correlated with behavior.

Behavioral results. Figure 4 indicates the mean thresholds following saline injections for each of the six groups at each response magnitude. An analysis of variance indicated that there was a significant main effect of treatment ($F=8.52$, $df=5/42$, $p<0.01$). Newman-Keuls analyses indicated that all of the groups, including the hippocampally lesioned group, were significantly more sensitive to shock than the untreated control group.

To assess the hypothesis that hippocampal lesion should reduce the effectiveness of 5-HTP in returning the thresholds toward normal, difference scores were calculated for each animal, i.e., for each response magnitude, the threshold after 5-HTP, minus the threshold after saline, was calculated. For each serotonin reduction method (septal lesion or PCPA), an

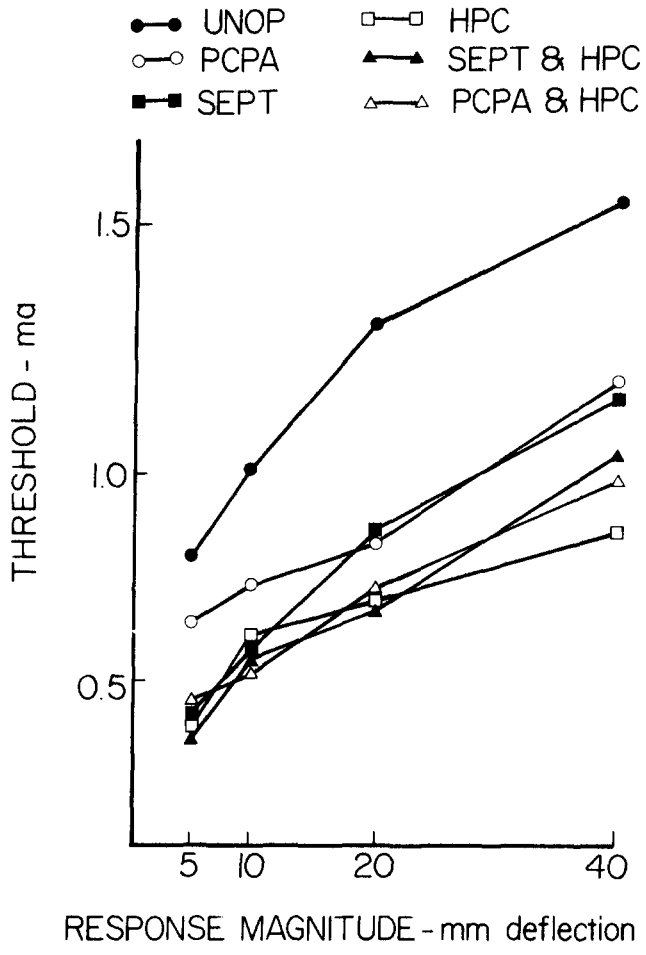

FIG. 4. Mean threshold intensity at each of four response amplitudes (after saline injection). All groups with serotonin depletion, hippocampal lesion, or both, are significantly more sensitive to footshock than controls. Note that hippocampal lesion effects are not additive with either septal lesion or PCPA.

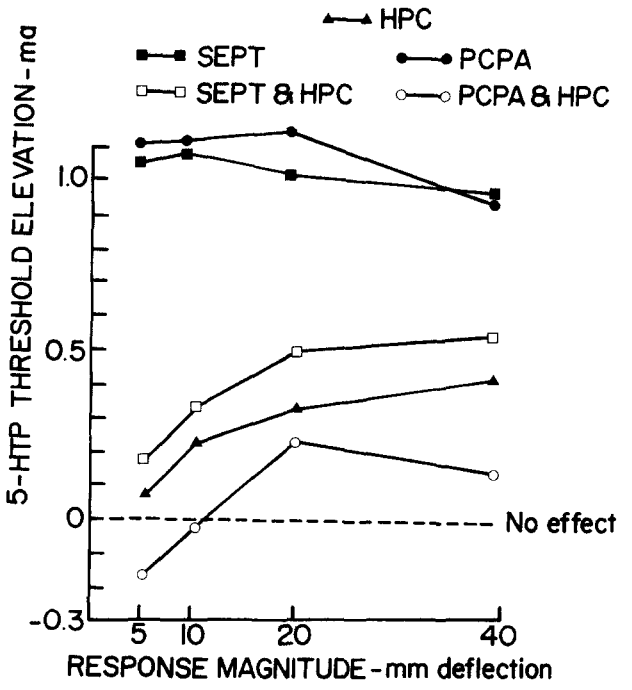

FIG. 5. Difference scores for threshold at each response amplitude under saline and 5-HTP for animals with PCPA alone and combined with hippocampal lesion, for septal lesion alone and with hippocampal lesion, and for hippocampal lesion alone. Higher difference scores represent larger effects of 5-HTP on shock threshold. The zero line represents complete lack of effect of 5-HTP.

analysis of variance was performed on the difference scores to compare the manipulations in animals with intact hippocampi with the same manipulation in animals with hippocampal lesion. In Fig. 5, therefore, the distance above the zero line represents the magnitude of the threshold change produced by 5-HTP, with the zero line indicating no effect of 5-HTP on footshock sensitivity. In animals given PCPA alone, 5-HTP clearly produces a dramatic change in the shock threshold at any response amplitude; nearly 1.0 mA greater footshock intensity is required to produce an equivalent response in the 5-HTP injected subjects as in the saline-injected control animals. In the animals which sustained hippocampal lesions in addition to identical PCPA regimens, an analysis of variance revealed significantly less recovery after 5-HTP ($F=49.22$, $df=1/14$, $p<0.01$); in fact, subjects with hippocampal lesions demonstrated no significant recovery after 5-HTP, in distinct contrast to the subjects with intact hippocampi.

As in the animals given PCPA, the septal lesioned animals recovered substantially following 5-HTP injection. When hippocampal lesions were combined with septal lesions, the magnitude of the 5-HTP effect was substantially reduced ($F=8.99$, $df=1/14$, $p<0.01$). There was, however, some effect of 5-HTP in the animals with hippocampal lesions; this effect was most evident at the higher response amplitudes, and was reflected in the significant interaction effect ($F=4.55$, $df=1/14$, $p<0.01$).

Figure 5 also shows the recovery produced by 5-HTP in subjects with hippocampal lesions alone. The with/without hippocampal lesion comparison used above is clearly inappropriate for comparing hippocampal lesions to controls for magnitude of 5-HTP effect, since the two groups differ significantly in shock thresholds prior to 5-HTP injection (Fig. 4). It is clear, however, that 5-HTP results in insubstantial recovery of hippocampally lesioned animals. In fact, such subjects remain significantly more sensitive to shock than undrugged control subjects ($F=6.92$, $df=1/14$, $p<0.025$).

DISCUSSION

The data of the present paper suggest that the serotonergic projection from the median raphe nucleus to hippocampus is important for the modulation of reactivity to footshock. Destruction of hippocampus markedly impairs the ability of 5-HTP to restore footshock sensitivity to normal levels following serotonin depletion by either PCPA or septal lesions, indicating that hippocampus is critical for normal action of 5-HTP.

Schlosberg and Harvey [26] have recently demonstrated that sensitivity to heat does not correlate with the circadian rhythm of hippocampal serotonin content, and have therefore concluded that hippocampal serotonin content is not significantly related to sensitivity to painful stimuli. The data of the present paper, however, demonstrate that hippocampus is critical for 5-HTP-induced recovery following serotonin depletion, and thus suggest that hippocampal serotonin content is a determinant of sensitivity to painful stimuli. While assay data indicating that hippocampal serotonin depletion (only) produces increased footshock sensitivity are not available, the present data strongly suggest that serotonin levels in some portion of hippocampus are important determinants of such sensitivity.

While the present data suggest the importance of the hippocampal serotonergic projection, they do not exclude the involvement of other serotonergic projections in the modulation of footshock sensitivity. The data in animals which sustained septal lesions and hippocampal lesions, or hippocampal lesions alone, indicated that the effects of 5-HTP were markedly reduced by hippocampal lesion, but were still present, suggesting that 5-HTP may also act on non-hippocampal sites, possibly in the spinal cord [21].

Since presence of intact hippocampi is clearly important for the action of 5-HTP, it is clear that serotonin may act in a more restricted area than all of forebrain to modulate footshock sensitivity. This emphasis on a more restricted projection also suggests an explanation for the failure of some serotonin-reducing manipulations, such as raphe lesion, to also increase footshock sensitivity. A manipulation which has a large average effect on forebrain serotonin, but a minor effect on some critical area within hippocampus, might also be expected to have a minor effect on footshock sensitivity.

Finally, the data of the present paper indicate that hippocampal lesions may produce associated increases in reactivity to footshock. This aspect of the data poses some interpretational problems for hippocampal lesion studies utilizing footshock as motivation. It is difficult to reject a priori the notion that hippocampally lesioned animals acquire a shuttle box avoidance response faster than unoperated animal [9] because they are more sensitive to the footshock. While not all hippocampal lesion studies must deal with this interpretational problem, further research is clearly required to adequately define the behavioral role of the serotonergic projection to hippocampus.

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