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# Septal Rage: Mitigation by Pre-Surgical Treatment with p-Chlorophenylalanine

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HARRELL, L. E. AND S. BALAGURA. *Septal rage: mitigation by pre-surgical treatment with p-chlorophenylalanine.* PHARMAC. BIOCHEM. BEHAV. 3(2) 157–159, 1975. – Destruction of the septum leads to a well known hyperirritability syndrome. However, the intensity of this syndrome is modifiable by certain presurgical treatments. Injections, prior to surgery of para-chlorophenylalanine (PCPA) for two days or insulin for five days has no effect on septal rage. However, injections of PCPA five days prior to surgery leads to a marked reduction in septal hyperirritability.

Septal lesions Recovery of function PCPA Insulin

UNTIL recently little work has been done on the modification of the recovery period which follows neurological damage. It has been demonstrated that this period is modifiable, at least in the feeding system, by certain pre- and postsurgical manipulations [1, 2, 3, 4, 9, 11, 12, 17]. However, little work on generalizing this phenomenon to other neurological systems has been performed. Since the hyperirritability which is subsequent to septal ablation disappears (recovery of normal emotionality) with the handling of the animal [5], we chose to study whether this behavior could be modified by presurgical treatment. Since insulin has been found to alter the recovery of feeding behavior following lateral hypothalamic lesions [2] and since para-chlorophenylalanine (PCPA) has been found to reduce septal rage when administered after surgery [7], these two compounds were chosen for surgical pretreatment.

## METHOD

### *Animals*

Forty-eight male albino rats were housed individually in a temperature controlled room (79°F ± 2°). Illumination was provided by standard flourescent ceiling lights (On at 0600, Off at 1800). Food and water were available ad lib throughout the experiment.

### *Procedure*

Following a week adaptation the rats were randomly assigned to 1 of 3 groups: an insulin pretreatment group, a 2 day pretreatment PCPA group, and a 5 day pretreatment PCPA group. For 5 days prior to surgery 8 animals in the insulin group were given 3 units of insulin in a volume of 0.2 ml subcutaneously at 8 a.m. and 8 p.m. ($INS_5$), while 8 others served as injection controls (C-$INS_5$). Eight rats were given intraperitoneal injections of PCPA (200 mg/kg; suspened in Steroid Suspending Vehicle) in a volume of 0.2 ml at 8 a.m. for 2 days prior to surgery ($PCPA_2$), the other 8 rats were injection controls (C-$PCPA_2$). For 5 days prior to surgery 8 rats were injected with PCPA (200 mg/kg) in a volume of 0.2 ml ($PCPA_5$), the remaining 8 rats served as injection controls (C-$PCPA_5$). All injections were performed under completely blind conditions and were discontinued 24 hr before surgery.

Following the injection series all animals received bilateral lesions of the septal area. These lesions were made under Nembutal (40 mg/kg) with the aid of a stereotaxic instrument, by passing anodal current of 3 mA for 30 sec through an insulex coated stainless steel electrode (0.5 mm in diameter). The stereotaxic coordinates with the incisor bar at zero were: 10.6 mm anterior to the interaural line, 0.8 mm lateral to the midsaggital sinus, and 5.2 mm below the surface of the dorsal cortex.

On the day after surgery all animals received behavioral testing to assess the degree of hyperirritability produced by the septal lesions. These tests, composed of four subjective rating measures (on a scale from 0 to 6), which have been employed in the past to rate septal rage [5], consisted of: (a) a poke to the animal's flank, (b) a poke to the animal's nose, (c) the animal's resistance to capture and (d) the animal's vocalization during handling. A fifth measure consisted of the animal's habituation to a poke to the flank. Animals were considered to have habituated when there was no response to three successive pokes. Behavioral testing was done for the first eight days following surgery. At the end of this time the animals were sacrificed, and histological verification of the lesion placement was made.

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## RESULTS

At the conclusion of the experiment only 38 out of the original 48 animals were included in the statistical computations due to either death at the time of surgery or to the incorrect placement of the lesions. Thus the $INS_5$ and C-$INS_5$ group was comprized of 12 rats (6 in each group), the $PCPA_2$ and C-$PCPA_2$ of 12 rats (6 in each group) and the $PCPA_5$ and C-$PCPA_5$ group contained 14 rats (7 in each group). Following surgery all rats demonstrated, to some extent, the typical hyperirritability (rage) which accompanies septal ablation. However, the intensity of the irritability depended upon the pretreatment the animal had received.

A comparison of all the saline controls revealed a high degree of rage following septal lesions (between 4 and 6 on the subjective rating scale). Furthermore, they responded repeatedly to the poke to the flank.

Comparison between the C-$INS_5$ and $INS_5$ animals and between the C-$PCPA_2$ and $PCPA_2$ rats revealed no differences in the four subjective measures. However, the $PCPA_2$ rats demonstrated a faster habituation to the flank poke than their controls (Analysis of Variance, $F(1,10) = 12.7$, $p<0.001$). This was not the case for the $INS_5$ groups (See Fig. 1, top and middle rows).

The animals pretreated with PCPA 5 days prior to surgery ($PCPA_5$), showed low scores on all the behavioral irritability tests except the poke to the flank (poke to nose, $F(2,12) = 3.5$, $p<0.05$; resistance to capture, $F(1,12) = 3.9$, $p<0.05$; vocalization $F(1,12) = 7.4$, $p<0.01$). Furthermore, they also demonstrated a faster habituation to the flank poke than their controls ($F(1,12) = 3.9$, $p<0.05$).

All six groups showed a gradual decrease in hyperirritability over the eight days following surgery as measured by the behavioral tests ($p<0.001$). Interaction effects between days and pretreatments were found only for the $PCPA_5$ animals and their controls (poke to nose, $F(7,84) = 2.4$, $p<0.025$; resistance to capture, $F(7,84) = 2.03$, $p<0.025$; vocalization $F(7,84) = 2.5$, $p<0.05$; habituation to poke, $F(7,84) = 4.6$, $p<0.001$).

No differences were found across groups in terms of lesion placements or to the extent of the tissues damaged. Lesions encompassed the whole septal area including the lateral and medial septum, the dorsal aspect of the diagonal bands of Broca and parts of the septal fornix (See Fig. 2).

## DISCUSSION

The present findings indicate that it is possible to attenuate the hyperirritability that follows lesions of the septum by the appropriate presurgical treatment. Thus pretreatment with PCPA, five days prior to surgery dampened the consequences of septal lesions, while pretreatment with PCPA two days prior to surgery, or with insulin had no effect.

A single injection of PCPA results in a progressive decrease in whole brain serotonin of rats [16]. It is known that such treatment does not interfere with catecholamine metabolism, but rather causes a reduction in brain serotonin by inhibiting the enzyme tryptophan hydroxylase [15], which converts tryptophan to 5-hydroxytrytophan (the rate limiting step in the formation of serotonin.

Behaviorally, the diminution of brain serotonin is accompanied by a slight increase of irritability and aggression in rats [16] and by an increase in spontaneous activity in rabbits [8]. Thus the behavioral measures obtained in the $PCPA_5$ animals after the discontinuation of the drug treatment can not be attributed to a behavioral depression. Fur-

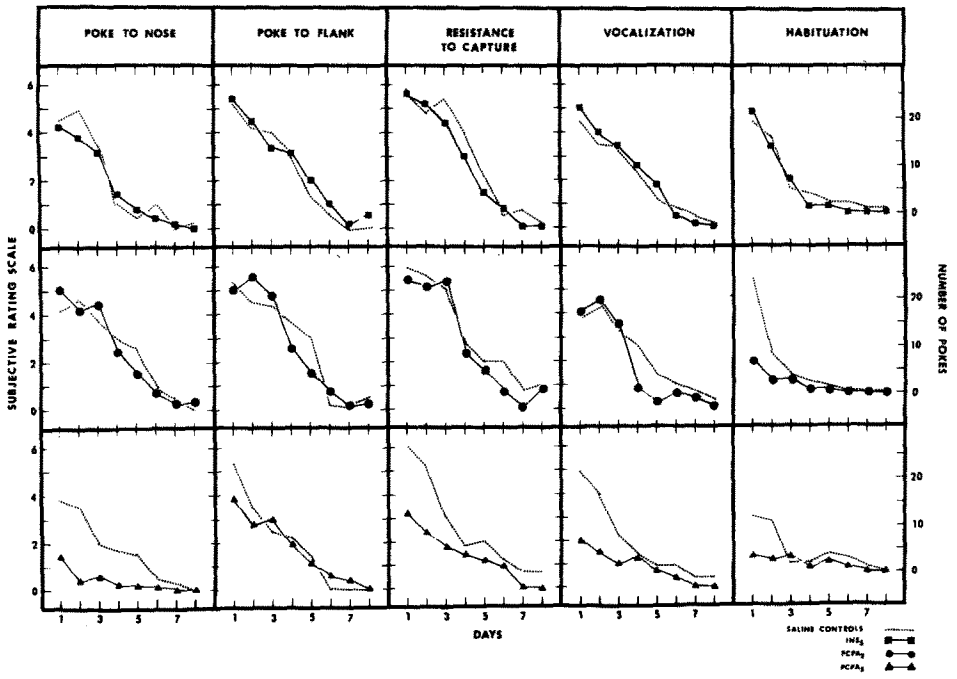


FIG. 1. Subjective ratings of rage and habituation to poke following septal lesions. First row: The effect of 5 days Insulin pretreatment. Second row: The effect of 2 days PCPA pretreatment. Third row: The effects of 5 days PCPA pretreatment.

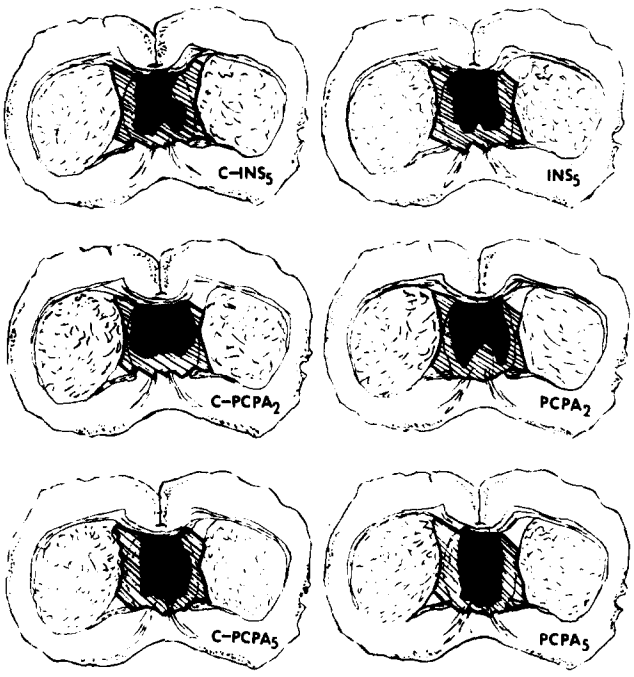


FIG. 2. Diagrammatic representation of the lesion placements. Black area = minimum extent of lesion. Striped area = maximum extent of lesion.

thermore, since the injection procedures that were employed led to a virtually depletion of serotonin within two days [15], it would be expected that the $PCPA_2$ animals would also demonstrate a reduction in septal rage if behavioral depression were the reason for the results. However, this was not the case.

Previously it has been reported that injections of PCPA produce an attenuation of the rage syndrome in rats with septal lesions [6]. However, it is hard to establish any relationship between the inhibition of the hyper-reactivity by PCPA and the brain content of serotonin since maximum sedative effects were observed within 2 hours, a time course quite different from that followed by the serotonin depletion. Thus the reduction in the septal hyperirritability produced by Dominguez and Longo [6] following septal lesions, was probably not due to the direct action of PCPA on septal serotonin.

Since PCPA has no effect on the levels of tryptophan hydroxylase in the septum [13], it can be hypothesized, in the present study, that the pretreatment with PCPA may have caused an alteration in another system functionally related to the septum which resulted in the reduced hyperirritability. The above contention is partially supported by the fact that septal lesions produce a 12–14% reduction in serotonin over a period of thirty-five days [14]. However, it is important to note that although five day pretreatment with PCPA was effective in reducing hyperirritability, two day pretreatment was not. This suggests that the systems mediating this phenomenon require a minimum amount of time and depletion before the effect is observed. Further support for a primarily serotonergic mechanism in this phenomenon is the fact the insulin, which has been postulated to influence the adrenergic system [18,19], pretreatment had no effect.

To summarize, the results of this study indicate that it is possible to modify septal rage by surgical pretreatment. However, the effect is specific to pretreatment for 5 days with PCPA suggesting that the brain mechanism mediating this effect is serotonergic in origin and requires a minimum amount of time for the PCPA to act.

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