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ROLE OF SEROTONERGIC MECHANISMS IN ANIMAL MODELS OF PREDATION

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Contents

Abstract

1. A short critical review of the role of serotonin in predatory attack is given.
2. Among factors determining the degree and type of psychopharmacological involvement are: species, drug, and dependent behavioral measure chosen as a representative index of predation.
3. One factor which may limit the actual involvement of serotonin is response non-specificity, i.e. the generalized disinhibition of behavior which is present after reductions in brain levels of this amine.
4. New data are presented concerning response specificity in two models of predation indicating this may pose an actual problem.

Key-words: aggression, attack behaviors, p-chlorophenylalanine, 5-hydroxytryptamine, indoleamines, predation, serotonin

Abbreviation: 5 hydroxytryptamine, serotonin, (5HT); p-chlorophenylalanine (PCPA)

1. INTRODUCTION

Predatory attack is a behaviorally and neurochemically distinctive form of interspecific aggressive behavior. Particularly in cats and rats, predation is behaviorally characterized by the absence of vocalization and autonomic arousal, by direct stalking approach to the prey stimulus, and by a stereotyped killing response generally involving the use of forepaws to position the prey and subsequent biting directed at the neck. Neurochemically, predation has been claimed to be cholinergically mediated (see for example Avis, 1974; Barr et al., 1976; Eichelman and Thoa, 1973; Reis, 1974), and both catecholaminergic (e.g. Katz, 1978) and serotoninergic (see below) influences have also been reported. The purpose of the present review is to specifically examine evidence regarding the role of serotonin in two widely used models of predation; feline and rodent interspecies attack.

2. THE MURICIDIAL MODEL

It should be noted at the outset that the bulk of studies that have positively identified a role (generally an inhibitory role) for serotonin in predation have made use of the muricidal model. The muricidal model uses the aggressive behaviors of the rat upon a mouse as an instance of predation. It is not the purpose of the present review to comment upon muricide as a representative predatory response, especially given previous reviews by O'Boyle (1974), Polsky (1975), and Rossi (1975). While some questions have been raised (Van Hemmel, 1975), the consensus of opinion is that at least some aspects of mouse killing may be appropriately investigated as predatory. Some of the major criteria for defining muricide as predatory are included in table one.

Table 1

Criteria for the inclusion of muricide with other instances of predatory behavior

1) Behavioral = quiet biting, stalking, biting directed at neck
2) Neuroanatomical = homologous limbic - hypothalamic-thalamic pathways
3) Motivational = presence of both some appetative factors and also excess killing; positively reinforcing aspects of prey in operant situations
4) Neurochemical = some equivalence of pharmacology across species, n.b. the presence of certain differences as well
5) Ethological = frogs (and to a lesser extent mice) are killed normally

2.1 Role of serotonergic system

Serotonin has been extensively investigated in the control of behavior.

One of the more widely used tools in the neuropharmacological assessment of serotonergic function is the synthetic amino acid PCPA (parachlorophenylalanine), an inhibitior of biosynthesis at the stage of hydroxylation. PCPA also is known to induce a state of phenylketonuria. In general the latter effects have been assumed to be behaviorally non significant for adult animals. The present section reviews initial and subsequent studies using PCPA. Other strategies involve direct intervention at a neuroanatomical level, through electrolytic or neurotoxic lesions, and those will be reviewed in series.

2.1.1 Effect of p-chlorophenylalanine and 5HT precursors

Early reports utilizing moderate to high doses of p-chlorophenylalanine (PCPA) suggested that lowering of brain serotonin was sufficient to increase the mouse killing response of normally nonmuricidal rats. The first report of this effect was a preliminary communication by Karli et al. (1969); however, neither procedural details nor precise drug dosages were reported. Sheard (1969) noted that both male and female non-muricidal rats given PCPA (as an ester, 320 mg/kg) and tested at 24 hr showed significantly elevated predation. This could be reversed by the administration of the immediate chemical precursor of serotonin, 5-hydroxytryptophan. This report also noted concomitant increases in other nonpredatory behaviors including sexual behaviors and irritability. The muricidal effect was confirmed by DiChiara et al. (1971) using isolated rats given 400 mg/kg of PCPA methyl ester, and tested at 36 hr. Again the facilitation proved to be reversible by precursor loading. Other more recent reports are in general agreement, at least with respect to the release of some form of aggression. McLain and Powell (1972), and later McLain et al. (1974) noted an increase in both frog and mouse killing over a three day test (dose = 316 mg/kg). Other positive reports include those of Sheard (1973) in which the behavioral effects of PCPA were compared with raphe lesions, and Kreiskott and Hoffmann (1975) who utilized stereoisomers of PCPA, Rolinski (1975) and Gibbons et al. (1978). The report by Gibbons et al. is of particular interest since it involved a much lower dose of drug, and a behaviorally specific facilitation of biting attack through the use of spontaneously muricidal rats.

Although several other reports are positive they suggest varying degrees of nonspecificity of response, Miczek and colleagues (Miczek et al., 1975) reported increases in an apparently "nonspecific" form of biting attack against mice or rat pups after high (3 x 300 mg/kg) doses of drug. Lower doses (3 x 100 mg/kg) and treatment with p-chloroamphetamine significantly lowered brain serotonin levels but did not affect predation. Reversal of muricide was possible but only with high doses of precursor. Paxinos et al. (1977) similarly noted only slight increases in muricide (28%) after four 350 mg/kg injections of PCPA. They also noted that preexposure could affect the development of attack, and that drug treatment induced muricide in conjunction with irritability and hyperdipsia. This apparent lack of response specificity seems to be a problem in other models as well, as discussed below.

2.1.2 Electrolytic Lesions

A second technique for investigating a role on serotonin has utilized electrolytic and pharmacologically specific lesions of serotonin containing cell bodies. While reports again are positive they are also characterized by certain inconsistencies with respect ot the specificity of the released response. Grant et al. (1973) noted that electrolytic lesions of the dorsal and median raphe nuclei caused a prolonged facilitation of muricide, the time course of which occurred in parallel with declines in forebrain serotonin levels. Vergnes et al. (1973) also reported that similar lesions produced muricide, however in only a small proportion of their total sample, and without a clear relationship to levels of serotonin or its metabolites. Sheard (1973), noted that while PCPA induced muricide, as previously

reported, electrolytic lesions of the midbrain raphe producing an equivalent lowering of serotonin were ineffective in this regard. Banerjee (1974) reported heightened irritability and muricide after raphe lesions, but only in selected rats. Rats which normally reacted to mice without aggression were not generally rendered aggressive. Yamamoto and Ueki (1977) noted that midbrain raphe lesions in either the dorsal or median raphe produced heightened defensive behaviors and muricide. Similar findings have been noted by Popova et al. (1975).

In a more recent study Waldbillig (1979) noted that the midbrain raphe nuclei may function differentially in the control of muricide. Radio-frequency lesions of the dorsal raphe were sufficient to induce muricide, while median raphe lesions did not produce attack. Moreover, a brain region at the border of the dorsal raphe had an opposite (inhibitory) effect upon muricide after lesion. This may explain some of the discrepancies in the above reports, since incursions into regions beyond the immediate borders of the raphe might produce variable results. It must be noted in passing that Yamamoto and Ueki (1977) did not find a similar degree of anatomic specificity in these earlier investigation.

2.1.3 Neurochemical Lesions

The neurotoxins 5,6 and 5,7 dihydroxytryptamine have been purported to specifically destroy serotonin cell bodies and terminals. Since these substances should be more specific than electrolytic lesions they may be expected to further clarify the role or roles of serotonin in predation. Breese et al. (1974) and Breese and Cooper (1975) noted an increase in muricide in rats injected intracisternally with 5,6 and 5,7 dihydroxytryptamine, respectively. This was not well correlated with reduced serotonin, and was accompanied by a variety of other behavioral effects. Hole et al. (1977) noted increased muricide and shock elicited boxing after 5,7 dihydroxytryptamine lesions of either the medial, or medial and lateral raphe nuclei. Finally Paxinos and Atrens (1977) noted increases in both muricide and irritability after 5,7 dihydroxytryptamine injections into ascending 5HT projections. These two effects did not correlate with each other, nor with feeding disruptions, nor did any effect correlate with serotonin depletion. Thus while the present studies implicate serotonin in predation and irritability, they do so in a rather limited fashion. Behavioral facilitation is accompanied by a variety of other forms of behavior and bears no direct relation to 5HT.

2.1.4 Dietary Manipulations

A converse and complementary strategy in identifying the effects of serotonin upon aggression involves the blockade of spontaneous muricide by increased serotonin. The technique of precursor loading attempts this by administration of either tryptophan or 5 hydroxytryptophan. Kulkarni (1968) has reported decreased muricide after precursor loading, and this has been verified in subsequent reports (Bocknik and Kulkarni, 1974) as well as by a second laboratory (Gibbons et al., 1978). It must be kept in mind, however, that tryptophan loading may produce drowsiness or somnolence.

Gibbons et al. (1979) have shown that a chronic low tryptophan diet induces muricide in non killing rats, and facilitates killing in normally muricidal subjects. These changes were accompanied by lowered brain serotonin and metabolites; both behavioral and biochemical changes were reversible by dietary replacement of the amino acid precursor.

While the bulk of reports have concentrated upon predation in the rat, both other muriod rodents and cats have also been examined to a lesser degree. McCarty et al. (1976) noted a decrease in the amount of predation in male and female grasshopper mice after 50 mg/kg/day PCPA for 5 days. They suggest their model may be a useful and ecologically valid alternative to

muricide, and their findings may point to an important species difference in attack mechanisms. It is important to realize in this regard that PCPA may not be equally effective or specific across species. Although serotonin was reduced in their study, other neurological effects i.e. reduction in brain weight were also present.

2.2 Additional data

Muricide does increase, however its specificity has been questioned. A possible control procedure for nonspecificity involves allowing subjects a simultaneous choice of goal objects (e.g. Katz, 1976). The present experiment utilized this strategy to further analyze the nature of PCPA induced aggression in the rat.

Subjects: Twenty rats were used. None spontaneously killed mice. Rats were individually housed with food and water continuously available, and 12h/12h lighting cycles (lights on - 0800-2000h).

Apparatus and Behavioral Procedure: Following an initial 3h home cage test to establish the absence of spontaneous muricide, subjects remained undisturbed except for normal cage maintenance (daily replacement of food, water, and cage bedding, and 4 exposures (8h each) to a testing arena (51 x 41 x 22 cm white plexiglas) for purposes of habituation. Two injections of p-chlorophenylalanine methyl ester HCl (150 mg/kg or 300 mg/kg per injection) were administered on consecutive days, and rats were tested 48h after the second injection. Testing procedures were analogous to those reported by Katz, 1976, for assessment of feline predation. A rat was habituated to the testing arena for an additional 4h. Both a novel mouse and a novel male rat, the latter of approximately equal weight to the experimental rat, were introduced into the arena. The following behavioral measures were utilized: 1) first choice for any form of behavioral interaction (inter vs. intra specific contact), 2) presence or absence of: predation, mounting, and non-predatory aggression (allogrooming either upright or sideways posture); a measure of irritability based upon the method of Ader (1969) was also incorporated into the experimental procedure.

Experimental Analysis was based upon contingency table analysis using the contingency coefficient C.

Results: For rats receiving either a low or high dose of PCPA, initial choice was bimodal. Fifty percent of each group initially contacted the mouse and the remainder initially contacted the rat. The contingency table is presented below.

It is evident that there is a significant correlation between predation and other nonpredatory forms of behavioral arousal. It might be noted that virtually all predatory animals also showed interspecific aggression when this was explicitly tested.

Table 2

Effects of PCPA upon muricide and other behaviors

	Attempted Mounting	Aggression	Irritability
Low Dose (n=10)			
Predation			
Present (n=2)	--	--	1
Absent (n=8)	--	2	2
High Dose (n=10)			
Predation			
Present (n=6)	5	5	6
Absent (n=4)	--	2	3
			C = .70
			p < .01

3. FELINE PREDATORY ATTACK

The attack behaviors of a cat upon a rat or mouse constitute clear and functionally significant instances of predation. Feline predation has been less well studied psychopharmacologically, and the range of manipulations present for muricide is not necessarily available in the literature upon feline predation. Nonetheless the available literature points to the potential existence of species differences and non specific effects.

3.1 Role of serotonergic system

Data concerning 5HT and predation in the cat are equivocal. Administration of between 75 and 300 mg/kg of PCPA to cats has been reported to initiate ferocious (apparently ragelike) attacks upon rats concomitant with hypersexuality and intraspecific aggression; however a later report from the same researchers claimed these effects were present to a much smaller degree if they were in fact present at all (Ferguson et al., 1970; Zitrin et al., 1970). Results based upon brain stimulated predatory behavior were also highly variable (MacDonnell et al., 1971; MacDonnell and Fessock, 1972). Some cats showed facilitated aggression while others showed no effect or debilitation. One common observation involved specifically increased ferocity of terminal attack elements (seizing and biting) for most subjects. This may suggest PCPA facilitates some but not all aspects of the feline predatory syndrome.

3.2 Additional data

Other manipulations, as noted above are not present. Given present inconsistency and lacunae in the literature there exists a clear need for the further investigation of neurotoxic lesions and dietary manipulations. Other strategies not widely used but of potential interest might involve the use of blockers such as methysegide and agonists such as quipazine.

To further study the role of serotonin in predation we have investigated the effects of PCPA upon attack using brain stimulation.

One advantage of brain stimulated aggression in cats is the range of quantifiable behaviors which may be readily and repeatedly elicited under constant conditions. Given the limited number of previous studies on PCPA and feline predation, the present report attempted to extend previous reports behaviorally, with specific emphasis upon the range of non-predatory aggressive behaviors that were present after treatment.

Methods:

Subjects: Four adult female cats weighing 2.0 - 3.5 kg were obtained from a local supplier (Bio-Medical Supply Inc., Freidensburg, PA), and were maintained on ad libitum food and water throughout the experiment. Normal day-night cycles of 14 hours daylight/10 hours darkness were maintained by natural and artificial lighting.

Surgery: Subjects were anesthetized with an intraperitoneal injection of 35 mg/kg sodium pentobarbital (Nembutal). Each subject was stereotaxically implanted with 12 stainless steel electrodes 0.25 mm in diameter insulated to the tip. Two indifferent electrodes were attached to stainless steel screws in the skull for purposes of monopolar stimulation. All electrodes were aimed at the lateral hypothalamic area (Snider and Neimer, 1964). Surgery was performed under aseptic conditions, and at the end of surgery, 150,000 units of Bicillin were administered intramuscularly. One week was allowed for recovery.

Apparatus: During testing the subjects were maintained in a 61 x 61 x 61 cm isolation chamber, with a constant level of 30dB masking noise provided by a ventilating fan and a white noise generator. One wall of the chamber consisted of a one-way mirror, through which all observations were made.

Procedure: Following surgery animals were tested for responding to stimulation. Electrical stimulation was provided by a Grass SD-9 stimulator and monitored across a 100 resistor in series with the animal on a Hewlett-Packard 122A oscilloscope. Stimulation consisted of 200 pulse/sec monophasic square waves of 1.0 ms duration and was delivered through a 2 uF capacitor in series with the animal to produce a biphasic pulse and minimize electrode polarization. All stimulation was presented in 15 sec trains with a 1 min interval between trains. Current levels were determined immediately prior to each stimulation by the presentation of a single 1.0 msec pulse. Only sites that consistently yielded attack characterized by quiet biting directed at the neck, and from which piloerection and autonomic arousal were absent were chosen for additional study. During initial and later aggression testing a small stuffed toy animal manipulated by means of a manually operated rod was maintained in constant irregular motion during the test session and served as an attack object for the assessment of component attack behaviors.

Two stages of testing were employed. These were establishment of a stable baseline of aggressive behavior under nondrugged conditions, and drug administration for two consecutive days, with behavioral testing for drug effects beginning immediately prior to the second day of drug injection and continuing for an additional two days. All test sessions were less than 1 hour in length, and separated from each other by 24 hours.

The drug effects were quantified in two manners, first by the determination of the stimulation threshold for attack and secondly by means of a rating procedure for the effects of the drugs on various components of attack to a constant suprathreshold stimulus.

Thresholds were obtained by starting with a clearly non-effective stimulus and incrementing the current on each trial by 0.1 mA until an attack was obtained. Both absolute threshold changes and probability of attack at (predrug) threshold served as dependent measures. Behavior in response to

suprathreshold stimulation was broken down into three categories defined as 1) approach (locomotion followed by paw or mouth contact with the attack object), 2) biting, 3) attack ferocity. Each category was rated on a 0-3 scale by two independent raters, one of whom was the experimenter and the second of whom was blind with regard to drug administration, current level, and the purpose of the experiment. The average score of both raters for a given behavior was used for statistical analysis.

The criteria established for scaling each category were as follows:

Approach: 0 - no observable locomotion, 1 - delayed locomotion, terminating in mouth or paw contact prior to or at offset of stimulation, 2 - short latency (2-5 seconds) and direct approach to attack object, 3 - immediate (2 seconds) locomotion and direct approach to attack object.

Biting: 0 - no oral contact with attack object, 1 - any oral contact with attack object involving jaw movement, 2 - one or more clearly defined bites with full opening and closure of mouth, 3 - repeated rhythmic biting with full jaw opening and closure.

Ferocity: A third measure was included as a control for non specific arousal. This was a measure of autonomic arousal as evidenced by hissing, spitting, and piloerection. Again a 0 to 3 score was used. 0 indicated an absence of all the above, and each subcategory contributed to a possible overall score in an interval fashion.

Drugs: Para-chlorophenylalanine methyl ester (Sigma C-3635) was administered 250 mg/kg in a normal saline vehicle solution to which 1 drop of polyoxyethylene mono-oleate (Tween-80; Sigma P1754) had been added for purposes of solvation. Drugs were injected intraperitoneally in approximately 5 cc vehicle solution. Drugs were administered twice, with a 24 hour interval separating the two injections.

Statistics: In order to assess drug effects across extended testing each response was analyzed across the testing period via a repeated measures analysis of variance. In addition, correlations r between experimenter and blind rater were calculated using Pearson's (Dixon and Massey, 1969).

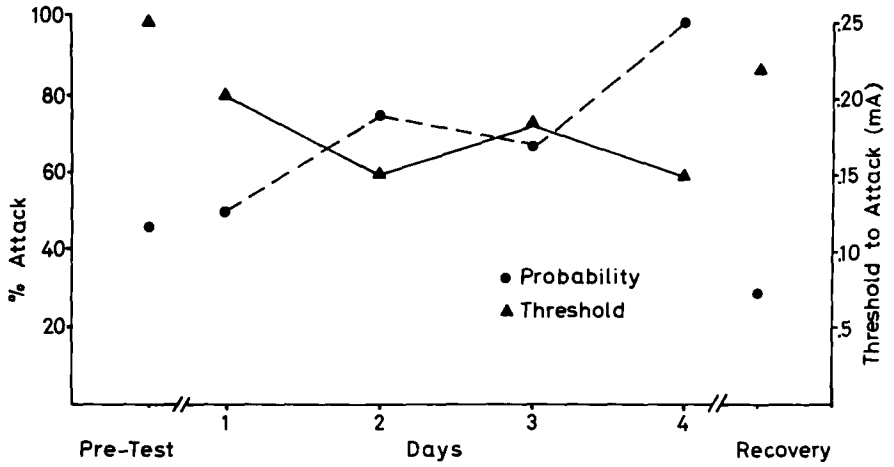

Fig. 1. Effects of PCPA upon brain stimulated predatory attack in the cat. Note probablity of attack is indicated on left most y-axis while threshold is indicated on remaining y-axis. Predrug score and post drug recovery are presented as left-most and farthest right points.

Table 3

Attack response categories after PCPA

Response Category	Score Pre	Post Injection: Day: One	Two	Three	F	p <
Approach	1.3	1.5	2.0	3.0	4.2	.05
Biting	1.5	2.0	2.0	1.5	1.5	.50
Ferocity	0.2	1.0	2.0	2.0	5.8	.02

(in all cases F is based on degrees of freedom = 3,12). Drug is administered immediately after testing upon pre and day one.

Histology: At the close of the experiment all subjects were injected with an overdose of Nembutal, and perfused first with a solution of normal saline and subsequently with a solution of 10% formaldehyde in saline. Brains were removed, sliced in 40 micron sections, stained and examined microscopically (Skinner, 1969). All sites which were used were located in the lateral hypothalamic area and perifornical area (Snider and Neimer, 1964).

Results: Inter-rater reliability was high across all measures (r =.9). It may be seen in Figure 1 that probability of attack was significantly increased while threshold was non significantly decreased by the drug manipulation. Approach was significantly increased (Table 1). Biting did not change significantly (Table 1). The measure of ferocity showed clear evidence of potentiation (Table 1). Four of four cats which did not normally hiss during attack displayed hissing. Likewise while piloerection was normally not present, it became prominent in the majority of subjects. It might be noted in passing that two normally friendly cats showed defensive behaviors or attack when approached by the experimenter. Recovery was essentially complete at 7 days (Fig. 1). All behavioral measures were likewise at control levels (data not presented separately).

4. DISCUSSION

Inhibition of brain serotonin increases attack behaviors and at least some of these are in fact prey directed. This apparently is a species specific response. Is it behaviorally specific as well? It has already been noted in a number of reports that irritability and sexual behavior increase with muricide. Thus, one possible alternative interpretation of the above effects rests with a generalized disinhibition of a variety of species specific behaviors. From our own experiments upon muricide and feline predation this seems to be the case. Granting this, a behaviorally specific role for serotonin in predation is more difficult to support. A review of the literature suggests some degree of nonspecificity is typically present after 5HT depletion. Among other changes are hypersexuality (Gessa and Tagliamonte, 1975; Dalhouse, 1976), irritability (Paxinos et al., 1977; Dalhouse, 1976), spontaneous intermale aggression (Gianutsos and Lal, 1975), shock elicited defensive behaviors (Conner et al., 1970; Sheard and Davis, 1976). Effects upon murine isolation induced aggression are equivocal (compare Hodge and Butcher, 1974; with Kostowski and Valzelli, 1974; Malick

and Barnett, 1976), and it appears that PCPA may have an aggression reducing effect upon septal hyperreactivity (Dominguez and Longo, 1969; Jones et al., 1976). Finally, pup killing is also increased by serotonin depletion (Miczek et al., 1975; Copenhaver et al., 1978).

A problem of interpretation is present then in these results. It might be questioned why a specific increase in predation is claimed. It might more prudently be claimed that serotonin depletion results in a generalized sensitization of a variety of motivated substrates.

At very least one must conclude that some degree of nonspecificity is present in the arousal response seen after PCPA. It is possible that testing circumstances contribute to the particular behaviors reported as increased and that both environmental and additional neurochemical mechanisms further act to shape predation. If only predation is tested for a misleading degree of specificity may be assumed. This testing with multiple tests of different types of aggressive behaviors is a preferred strategies, offering internal controls for types of aggressive behavior altered by drug treatment.

We have previously noted that cholinergic stimulation results in the activation of a general aggresive substrate which includes elements of affective and predatory attack. It is possible to view serotonin as playing a converse general inhibitory role. While this limits the sort of single transmitter single function analysis of some of the above reports it offers an alternative view with a number of potential levels of behavioral control.

5. CONCLUSION

Understanding the role of serotonin in aggression, and particularly in predation and other aggressive behaviors, is potentially quite important. At present, however, both the neurochemical, anatomical and behavioral involvement of this amine must be taken as an open question demanding additional scrutiny.

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