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BRIEF COMMUNICATION

Central Catechol- and Indolamine Systems and Aggression[1]

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MCLAIN, W. C., B. T. COLE, R. SCHREIBER AND D. A. POWELL. *Central catechol- and indolamine systems and aggression.* PHARM. BIOCHEM. BEHAV. 2(1) 123–126, 1974. – Separate groups of rats were treated with alpha-methyl-tyrosine (AMT), para-chlorophenylalanine (PCPA), or saline. Subsequently, inter-species attack and shock elicited aggression (SEA) were assessed. Although neither AMT or PCPA affected SEA, PCPA decreased the latency of frog attack, and had a negligible effect on frog attack frequency. Both drugs increased the frequency of mouse attack. These results suggest a different neurochemical basis for different kinds of aggression.

Norepinephrine Serotonin Alpha-methyl-tyrosine PCPA Shock-aggression Mouse and frog attack Rats

IT HAS been suggested that aggression is a heterogenous class of behaviors which are only superficially similar [8]. In support of this thesis are experiments employing several different models of aggression which show that such models are differentially related to both physiological and situational variables e.g., [1, 7, 8]. However, a clear understanding of the extent to which different neurophysiological and neuroanatomical substrates are related to different manifestations of aggression depends upon studying various models in the same animals. Few such experiments have heretofore been performed.

In the present experiment we sought to determine whether shockelicited aggression (SEA) and mouse and frog attack were differentially related to the administration of drugs which affect the brain levels of (a) the catecholamines (CA), and (b) serotonin (5–HT). Alpha-methyltyrosine (AMT) inhibits the rate limiting step in the synthesis of norepinephrine (NE) and dopamine (DA) by interference with tyrosine hydroxylase, an enzyme which catalyzes the synthesis of DOPA from tyrosine [9]. Para-chlorophenylalanine (PCPA) similarly inhibits the synthesis of 5–HT, also by blocking the rate limiting step, which involves the synthesis of 5-hydroxytryptophan from tryptophan [4]. Thus the effects of PCPA and AMT were studied upon (a) shock-elicited aggression, and (b) frog and mouse attack.

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METHOD

Animals

Seventy-eight 100-day-old male Long-Evans hooded rats were divided into 2 groups of 20 experimental and 2 groups of 18 and 20 control animals.

Apparatus

Mouse and frog attack were measured in the rat's home cage. Shockelicited aggression (SEA) was assessed in a Scientific Prototype animal chamber with inside dimensions of 23.5 × 20.3 × 29.8 cm, housed inside a larger sound attenuated compartment with a one-way mirror. A white noise background of 75 dbl SPL was continuously presented through an overhead speaker.

Procedure

One group of 20 experimental rats was administered a single dosage of 316 mg/Kg D–L PCPA methyl ester, ip. A second group of 20 animals was administered three daily dosages (separated by 4 h each) of 50 mg/Kg D–L AMT methylester over three consecutive days. These dosage regimens were based upon prior experiments [4,9] which showed that they produced maximum central depletion of CA and 5–HT, accompanied by minimum toxic side effects. A third group of 18 rats was administered a control saline vehicle. A fourth group of 20 naive uninjected animals, which had been maintained in our laboratory for the same length of time as animals in the present experiment, but which had no experience with either shock or frog attack during the experiment, were also tested for mouse attack. Both frog attack and shockelicited aggression were measured daily over three days, 12 h after the first dosage of AMT was administered. On the second day 48 h after the first drug administration and after frog attack and SEA measurements were made, a mouse was placed in the home cage of each animal and the attack behavior of the animals observed for 10 min. Ten hours later the mice which had not been killed were removed. SEA sessions were 5 min in duration. Paired animals were placed in the experimental chamber and 100 2 mA footshocks of 0.5 sec duration administered at a frequency of 20 shocks per min. Observers, who were blind with respect to experimental treatment, observed the animals behavior. A fight was defined as a striking, lunging or biting movement made by either one or both animals [7]. After decapitation on the third day, whole brain assays of norepinephrine and 5–HT were performed according to the method of Maickel, *et al.* [6].

RESULTS

The animals in the PCPA group showed a pronounced decrease in latency of frog attack compared to the AMT and saline animals. These differences can be seen in the left side of Fig. 1, in which the mean reciprocal of latency in seconds is plotted for each group over each of the three daily sessions. PCPA latencies were significantly less than the AMT and saline latencies during both the second and third sessions of the experiment based on the Wilcoxon

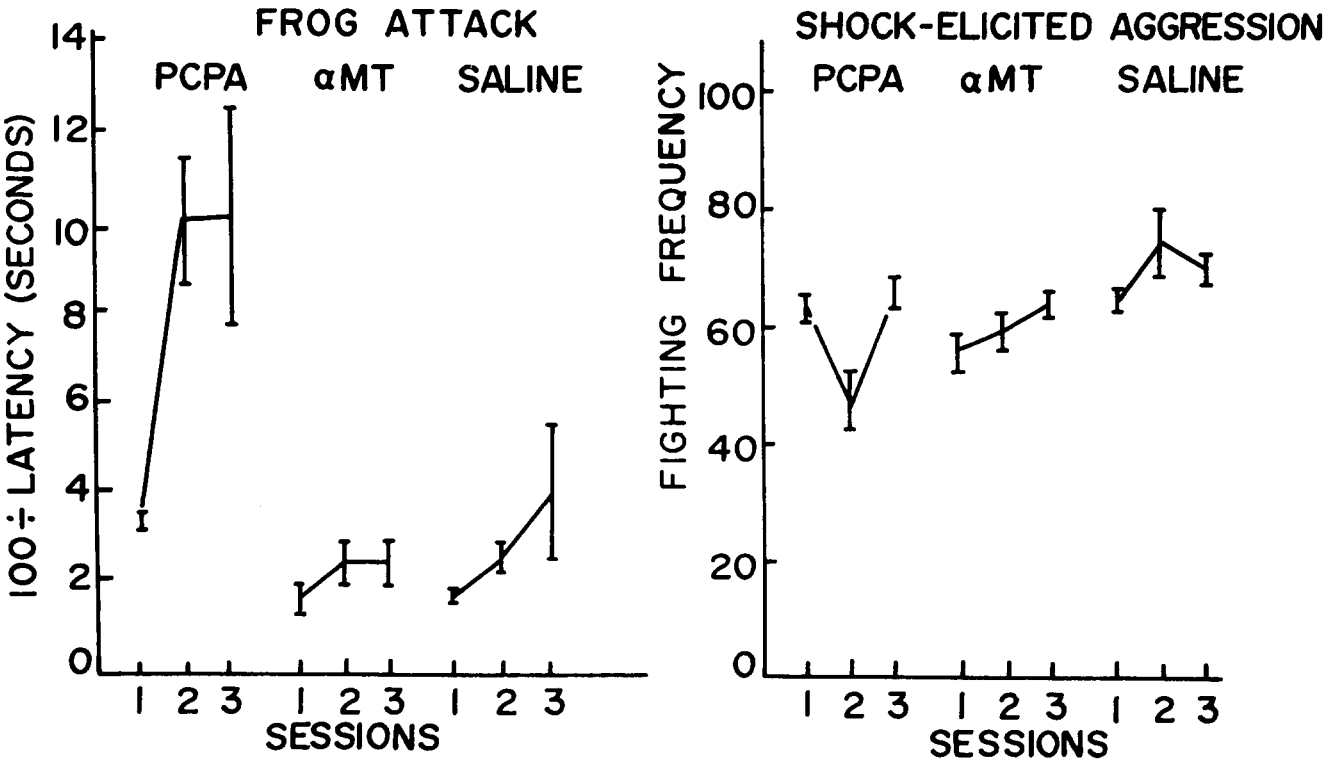

FIG. 1. Frog attack 100/latency scores (left) and frequency of fighting in response to shock (right) of rats injected with (a) parachlorophenylalanine, (b) alpha-methyl-tyrosine, or (c) saline on three consecutive daily sessions. Brackets indicate standard errors.

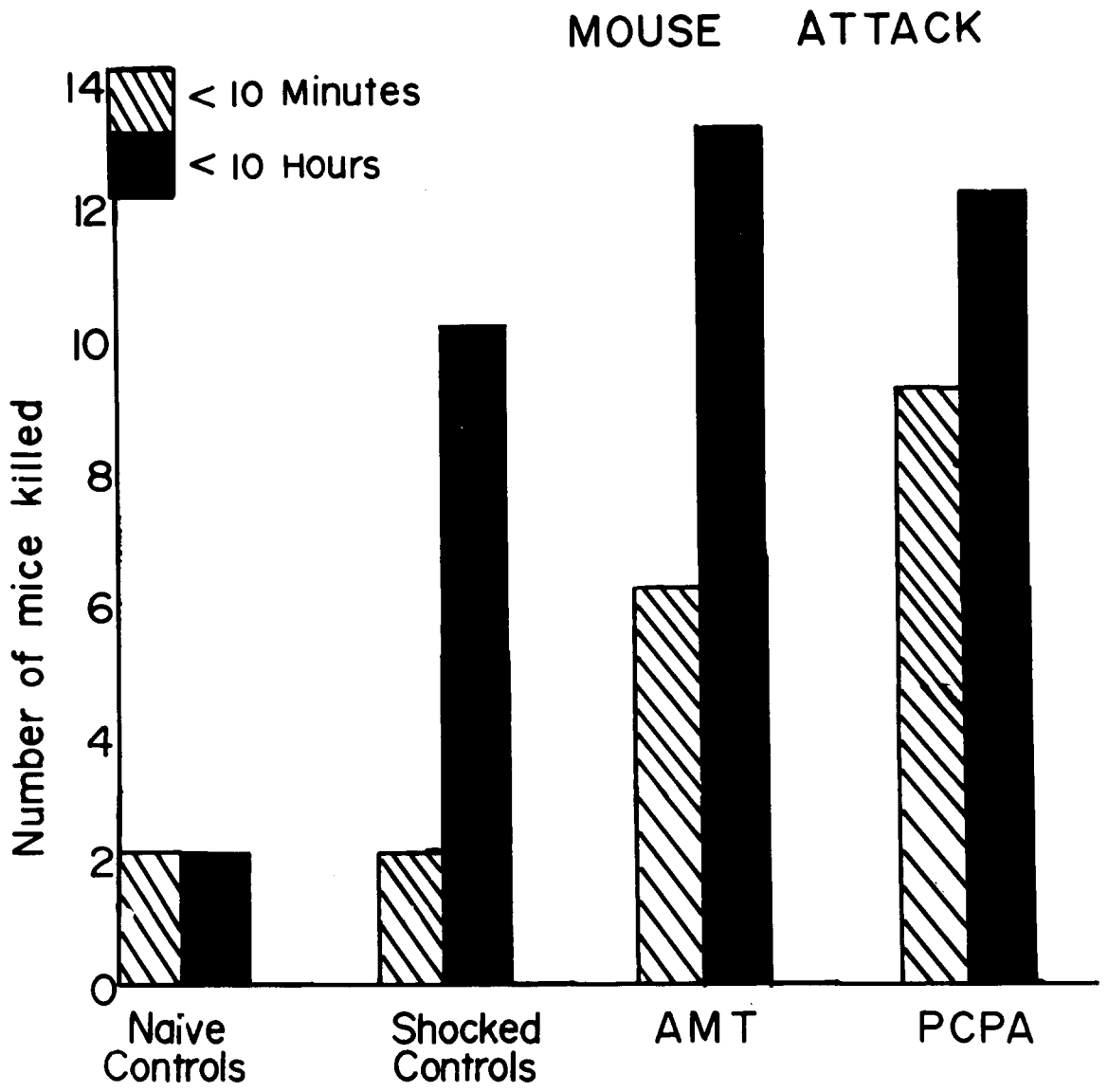

FIG. 2. Number of mouse attacks by rats during first 10 min and first 10 h after introduction of mouse. Separate groups of animals were (a) naive with respect to mouse attack and shock (naive controls) (b) had shock-fighting and frog attack experience (shocked controls) and injected with saline, or (c) were similar to shocked controls but injected with alpha-methyl-tyrosine (AMT), or (d) parachlorophenylalanine (PCPA).

Rank Sum Test ($p<0.01$) [11]. However, latency scores of the AMT and saline animals were not significantly different. A similar comparison of the SEA scores (also shown in Fig. 1), revealed no significant differences between any of the three groups. However, the latter were all within the range described by previous investigators e.g., [7].

The frog attack latency scores for the individual animals which were paired during SEA sessions were averaged, and the association between these scores and the SEA scores determined by computing product moment correlation coefficients for each of the three group which received these treatments. However, these coefficients were significant in only one of nine possible comparisons (r = -.79; AMT group; Day 1).

The frequency of mouse attack was assessed during the first 10 min as well as after 10 h had elapsed. These attack frequencies are shown in Fig. 2. Also indicated in this figure are the number of rats from the group of 20 naive unshocked animals drawn at random from the Long-Evans hooded colony in our laboratory. A comparison of animals which killed in the first ten minutes showed no differences between these naive unshocked control animals and the shocked-control animals. Both groups included two rats which killed in the first 10 min. However, the PCPA treated animals killed 9 and the AMT animals killed 6 of 20 mice during the first 10 min. There were only minor differences between the number of mice killed after 10 hr in any of the groups which had previously received SEA and frog attack

experience (AMT = 13, PCPA = 12, and Saline = 8). However, these data contrast with the non-shocked control rats which killed only 2 mice during the first 10 min and none thereafter. A chi-square analysis of the mouse attack data was significant for both the 10 min and the 10 hr frequencies (chi-square = 10.29, $p<0.01$ for 10 min and 31.58, $p<0.01$ for 10 hr). Bio-assay of whole brains revealed the mean depletion of 5-HT and NE in the experimental groups to be 53% and 40%, respectively, of the vehicle treated animals.

DISCUSSION

PCPA in the present experiments resulted in decreased frog attack latencies and high frequencies of mouse attack relative to control animals. Since the brain levels of 5-HT were almost half that of control animals at the end of the experiment, this increase in attack behavior is probably related to a central inhibitory serotonergic system. Other investigators have also found serotonin manipulations to affect mouse attack e.g., [2]. Although CA depletion produced increases in mouse attack, as others have reported e.g., [5], it had no effect upon frog attack latencies. The latter finding suggests that frog and mouse attack are perhaps also controlled by different biochemical variables.

The present results also confirm the finding of Conner and associates [1] that PCPA administration does not affect SEA. In addition, the present results showed that AMT has no effect on SEA frequencies. Thus, in contrast to mouse and frog attack, these results suggest that aggression elicited by painful stimulation is unrelated to central noradrenergic and serotonergic systems. The lack of a significant correlation between SEA and frog and mouse attack scores in 8 or 9 comparisons further suggest the independence of these two systems of behavior. Although SEA may be representative of a more general class of defensive behaviors, controlled by a complex set of biochemical variables, the present results suggest that CA and 5-HT are not importantly involved.

However, the present results conflict with recent experiments e.g., [3,10] from the NIMH Laboratories, which suggest that SEA is mediated by a central CA system. Although the behavioral methodologies of the present study and the NIMH experiments were similar, the latter interfered with central noradrenergic systems by the administration of 6-hydroxydopa, and 6-hydroxydopamine (6-OHDA). Central 6-OHDA administration results in lower CNS levels of CA, as does AMT, but it produces this effect by destruction of NE and DA terminals rather than interference with NE and DA synthesis. In the absence of a full understanding of how these various substances produce their effects, however, a complete explanation of these discrepancies awaits further research.

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