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Testosterone Manipulations: Effects on Ranacide Aggression and Brain Monoamines in the Adult Female Rat[1]

BRUCE K. BERNARD[2]

Section of Pharmacology and Toxicology, University of Connecticut, Storrs, CT 06268

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BERNARD, B. K. *Testosterone manipulations: effects on ranacide aggression and brain monoamines in the adult female rat.* PHARMAC. BIOCHEM. BEHAV. 4(1) 59–65, 1976. – The effect of testosterone propionate on ranacide (frog-killing) behavior and brain norepinephrine (NE), dopamine (DA) and serotonin (5-HT) levels was determined in 40 female Wistar rats. Adult rats were screened for frog killing behavior on the basis of a single 30 min testing session. Aggressors were defined as animals which attacked or killed during this session while nonaggressors failed to do so. Using either aggressors or nonaggressors, testosterone and sesame oil equally increased aggressive behavior as measured in a second 30 min testing session. Biochemical analyses indicated that testosterone treated animals had significantly higher brain NE and NE/5-HT levels. Aggressors, testosterone or sesame treated had higher NE/5-HT ratios. Whole-brain levels of DA and 5-HT and the DA/5-HT ratios were unaffected. It is concluded that the elicitation of ranacide in the adult female rat is not androgen dependent nor is this behavior functionally related to the observed differences in brain noradrenergic/serotonergic levels. This study provides additional evidence that ranacide is a type of predatory aggression and yet presents data which may be at variance with the classic monoaminergic theory of aggressive behaviors.

Ranacide aggression Testosterone Brain monoamines Norepinephrine Dopamine Serotonin

THE investigation of a functional relationship between brain monoamines and aggressive behavior has simultaneously been advanced and stymied by recent reports demonstrating the heterogenity of models of aggressive behavior. Classificatory schemes of aggressive behavior have emphasized either the stimulus which elicits the behavior [30] or the neurological basis of the behavior itself [32]. The eliciting-stimulus theory separates aggressive behavior on the basis of external (eliciting) stimuli, and the somewhat limited neurological and endocrinological data available at the inception of the schemata. Thus predatory aggression, which is one of six proposed subclasses, is thought to be nonadrogen dependent and can be elicited by stimulation of the lateral hypothalamus. This behavior can be differentiated from inter-male aggression, for example, since the latter is androgen dependent and involves the septal brain region [30].

The neurological model stresses the neuroanatomical and pharmacological distinction between two subclasses of aggressive behavior: predatory and affective [32]. Predatory aggression can be enhanced either by pharmacological agents which increase the efficacy of the cholinergic system or by electrical stimulation of the ventral medial tegmentum. This behavior is not associated with the autonomic activation components seen in affective aggression. The pharmacological characteristics associated with affective aggressive behavior are precisely the opposite of that just described [31]; that is, inhibition of the cholinergic system results in enhancement of affective aggression as does electrical stimulation of the brain central gray matter.

In a recent publication, the present author enumerated the presently available evidence which indicated ranacide (frog-killing) was a type of predatory aggression [6]. Furthermore, the experimental evidence reported therein indicated that ranacide was nonandrogen dependent in either naturally aggressive or nonaggressive adult male rats. In a more recent publication dealing with androgen dependency of aggressive behavior, Bernard and Paolino [12] demonstrated the androgen dependency of shock-induced aggression and related the time-dependent nature of this effect to previously reported time- and androgen-dependent brain monoaminergic changes [11]. Thus, shock-induced aggressive animals had higher brain norepinephrine levels compared to brain serotonin levels (NE/5-HT ratios) than did non-aggressive animals.

The purposes of the present experiments were two-fold: first, to determine if the nonandrogen dependency of ranacide behavior as seen in adult male rats could be

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extended to either naturally aggressive and/or nonaggressive adult female rats; secondly, to determine if these aggressive and/or nonaggressive female rats differed with regard to brain levels of serotonin (5-HT), norepinephrine (NE), dopamine (DA) or brain NE/5-HT ratios and what effect exogenous testosterone administration had on these neurochemical indices. It was expected that the simultaneous determinations of ranacide behavior and neurochemical effects might provide a basis for relating these changes in a functional manner.

GENERAL METHOD

Animals

Adult female Wistar rats, 70–80 days of age, were housed 5–7 per group in stainless steel cages (24 x 17 x 10 in.) and maintained on ad lib food and water for the duration of the experiment. Rooms were kept on a 12 hr light-dark cycle (light from 0600–1800) and maintained at a temperature of approximately 71°F. Animals were left undisturbed for 2 weeks prior to initial screening.

Ranacide Screening

After 2 weeks of acclimation, each animal was placed in a smaller testing cage (11 x 8 x 8 in.). Approximately 24 hr later the rat was forced to the back half of the chamber by inserting a masonite board; a frog (*Rana pipens*, 3–3½ in. in length) was inserted on the opposite side of the masonite divider. The divider was removed and the latencies until the first attack and death of the frog were recorded. The frog was removed either immediately after its death or at the end of the 30 min testing session. Following this screening session, the rats were placed into new cages (5–7 per group) according to the behavior exhibited (aggressive or nonaggressive). These groups were then subjected to various hormonal treatments which were then followed by a second, posttreatment ranacide testing session. The latencies to attack and kill were again measured and compared to the preinjection ranacide testing session.

EXPERIMENT 1

Procedure

Rats were screened (Trial 1) for ranacide behavior as described above. Following the screening session, the rats which did not attack or kill during this 30 min testing session (nonaggressive, NA) were divided into 2 subgroups. The first of these subgroups (NA + T) received 15 subcutaneous injections of testosterone proprionate (Oreton, 200 μg in 0.1 ml sesame oil vehicle) on alternate days for 30 days. This sequence has been shown to be sufficient for maintaining masculine behavior in the adult male rat [5]. The second group (NA + S) received only sesame oil injections for the same period of time. Twenty-four hr following the last injection, both the NA + T and NA + S groups received an additional ranacide testing session (Trial 2). Latencies to first attack and kill were again measured and compared to preinjection sessions. All animals were returned to their group cages following this posttreatment session and continued on the appropriate hormonal regimen. Seventy-two hr later all animals were decapitated, their brains rapidly removed and crushed between two layers of dry ice. The solidified brains were immediately weighed to the nearest milligram and homogenized in 10 volumes of acidified butanol. The catecholamines, norepinephrine (NE) and dopamine (DA) and the indoleamine, serotonin (5-HT) were extracted and analyzed using a modification of spectrophotofluorometric analyses previously described [2, 16, 29].

Results

The effects of hormonal manipulations on the posttreatment aggressiveness in these initially nonaggressive animals can be seen in Table 1. These results indicate that on the posthormonal ranacide screening session (Trial 2) both the sesame and testosterone treated rats decreased their latency to attack (6.33 and 9.53, respectively) as compared to pretreatment behavior (>30). Yet when a comparison is made using the nonparametric Mann Whitney U test [33] there was no significant difference between groups (NA + T and NA + S, Trial 1 vs Trial 2; $n_1 = 5$, $n_2 = 16$, $U = 30$, $p > 0.1$). Further analysis of these data in terms of either the number of sesame or testosterone treated animals which attacked following injections (5/5 and 12/16 respectively) failed to reveal a testosterone effect. A similar conclusion was obtained when analyzing for killing behavior (2/5 and 4/16, respectively). Thus, exogenous testosterone injections did not increase the ranacide behavior in these adult and initially nonaggressive female rats to a greater extent than that observed in the vehicle controls animals.

TABLE 1

FAILURE OF TESTOSTERONE ADMINISTRATION TO ALTER ATTACK BEHAVIOR IN NONAGGRESSIVE FEMALE RATS

	Latency to Attack		
Groups	Trial 1		Trial 2
Nonaggressive + Sesame Oil	>30.00*	[5]	6.33 (13–2)
Nonaggressive + Testosterone	>30.00	[16]	9.53 (>30–.3)

*Median latency to attack (min)
( ) Range of values (min)
[ ] Number of animals/group

The biochemical effects of these hormonal manipulations varied depending upon the monoamine under consideration. The data shown in Table 3 were analyzed using two-way analyses of variance [38] and revealed no alterations in either brain serotonin (5-HT) or dopamine (DA) levels induced by testosterone in these nonaggressive rats. However, similar analyses of brain norepinephrine levels revealed a significant increase in the testosterone treated animals ($p < 0.01$) when compared to sesame controls (Table 4). Thus, although testosterone administration failed to increase the aggressiveness of nonaggressive female rats and also failed to alter whole-brain levels of

either 5-HT or DA, there was a significant increase in whole-brain NE.

This experiment demonstrates that exogenous testosterone administration will not induce aggression in adult female rats (which are not normally aggressive) beyond that observed in the sesame injection control rats. As has been previously postulated [6], while testosterone may not initiate new behavior, it may have an effect on the modulation of behavior already present in the behavioral hierarchy of the animal. In order to test this hypothesis, a second experiment employing adult female rats which spontaneously killed frogs was performed.

EXPERIMENT 2

Procedure

Rats were screened for ranacide behavior as previously described. Following the screening session (Trial 1), rats which attacked or killed during this 30 min test (aggressive, A) were divided into two subgroups. These subgroups received either testosterone proprionate injections (A + T) or vehicle control injections (A + S) as previously described. Twenty-four hr following the last injection, both the A + T and A + S groups received a second (posttreatment) aggression testing session (Trial 2). Latencies to attack and/or kill were measured and compared to preinjection times. Following the behavioral testing, both subgroups were treated similar to the animals in the NA groups; whole-brain monoamine levels were determined 72 hr later using a spectrophotofluorometric analysis.

Results

The results of the posthormonal behavioral testings in these naturally aggressive adult female rats can be seen in Table 2.

TABLE 2

FAILURE OF TESTOSTERONE ADMINISTRATION TO ALTER THE MEDIAN LATENCY TO ATTACK OR KILL IN AGGRESSIVE FEMALE RATS

	Latency to Attack		
Groups	Trial 1		Trial 2
Aggressive + Sesame Oil	10.25* (29–5)	[9]	9.25† (14–2)
Aggressive + Testosterone	9.58 (15–1)	[8]	2.42‡ (27–1)

*Median latency to attack or kill (min)
†$p<0.02$ Trial 1 vs 2
‡$p<0.035$ Trial 1 vs 2
( ) Range of values
[ ] Number of animals/group

These data were analyzed using both the nonparametric Sign Test and the Wilcoxon Matched-Pairs Sign Rank Test [33] which employs direction of changes and rank order quantification of these changes, respectively. The results indicated that sesame oil treated animals had a significantly lower median latency on the posttreatment ranacide session (Trial 2) as compared with their pretreatment latencies ($p<0.02$ and $p<0.01$ for each test). Sign Test analysis of the testosterone treated animals' latencies showed a similar decrease ($p<0.035$); the Wilcoxon Matched-Pairs Sign Rank Test did not reach significance because of a large increase in the latency of one animal. The trends were compared using a Mann-Whitney U Test and there was no significant difference between the effect of treatments on ranacide aggression ($n_1 = 8$, $n_2 = 9$, $U = 34$, $p>0.1$). These behavioral results support the findings of the first experiment using nonaggressive rats. Thus, exogenously administered testosterone appears to be neither an initiator nor a promoter of ranacide aggression in the adult female rat.

The effect of testosterone on whole-brain serotonin (5-HT) or dopamine (DA) levels in naturally aggressive female rats is similar to that already seen in nonaggressive female rats. Table 3 contains these data; two way analyses of variance revealed no alteration in these monoamine levels in the testosterone treated aggressive animals. Whole-brain NE levels in these aggressive animals were not altered by testosterone administration (Table 4) as it was in the nonaggressive animals. This failure of testosterone to increase NE levels in naturally aggressive adult female rats may be of little importance since the aggressive animals receiving sesame oil already had higher NE levels than the nonaggressive controls (Newman-Keuls, $p<0.05$). Thus, these results may simply reflect the inability of testosterone to raise NE levels beyond a specific point. Aggressive and nonaggressive testosterone treated animals had elevated NE levels when compared to sesame controls but did not differ significantly from each other.

The result of this overall increase in NE levels (278.7 vs 298.6) in testosterone treated animals is also reflected by significant alterations in relative aminergic dominance (Table 5). Thus, aggressive animals had higher NE/5-HT ratios than the nonaggressive animals, $F(1,12) = 6.61$, $p<0.02$, and testosterone treated animals had higher levels than vehicle control animals, $F(1,12) = 4.65$, $p<0.05$. These effects were additive and there was no significant statistical interaction between the two factors.

DISCUSSION

The behavioral results of these experiments extend to female rats, the previously reported hypothesis that alteration in testosterone levels could not be employed to alter ranacide behavior in the adult male rat [6]. After that series of published experiments which employed both castration and exogenous testosterone administration, this author came to the conclusion that ". . . testosterone is neither an initiator nor a promoter of ranacide behavior in the adult male rat, nor an inhibitor of ranacide in established killers." These findings may now be broadened to include adult rats of both sexes. Thus, female rats which failed to attack or kill frogs during an initial ranacide screening session did not kill or attack with any greater rapidity after receiving exogenous testosterone than the animals receiving sesame control injections. Similarly,

TABLE 3

EFFECT OF TESTOSTERONE ADMINISTRATION ON WHOLE-BRAIN SEROTONIN AND DOPAMINE LEVELS IN AGGRESSIVE AND NONAGGRESSIVE FEMALE RATS

Groups	Brain Monoamine Levels* Serotonin	Dopamine
Nonaggressive +		
Sesame Oil	558.9 ± 34.87 [5]	138.28 ± 23.59 [5]
Testosterone	573.7 ± 24.8 [4]	1424.8 ± 47.4 [4]
Aggressive +		
Sesame Oil	529.7 ± 15.7 [3]	1460.9 ± 17.02 [5]
Testosterone	515.0 ± 19.4 [5]	1320.3 ± 53.3 [5]

*Data expressed as ng amine/g tissue; mean ± standard error. Amine levels were analyzed using ANOVA.
[ ] Number of animals/group

TABLE 4

EFFECT OF TESTOSTERONE ADMINISTRATION ON WHOLE BRAIN NOREPINEPHRINE LEVELS IN AGGRESSIVE AND NONAGGRESSIVE FEMALE RATS

Treatment	Behavior Nonaggressive	Aggressive	Combined
Sesame Oil	270.3 ± 5.84* [5]	287.1 ± 3.43§ [5]	278.7 ± 4.25 [10]
Testosterone	305.5 ± 6.18† [4]	293.1 ± 2.23‡ [5]	298.6 ± 3.67[a] [9]
Combined	285.9 ± 7.36 [9]	290.1 ± 2.34 [10]	

*Data expressed as ng amine/g tissue; mean ± standard error. Amine levels were analyzed using ANOVA followed by Newman-Keuls.
†$p<0.01$ Nonaggressive testosterone vs nonaggressive sesame
$p<0.05$ Nonaggressive testosterone vs aggressive sesame
‡$p<0.05$ Aggressive testosterone vs nonaggressive sesame
§$p<0.05$ Aggressive sesame vs nonaggressive sesame
[a]$p<0.001$ Testosterone vs sesame
[ ] Number of animals/groups

female rats which were naturally aggressive did not differ from control animals when tested after receiving testosterone supplements. One can speculate on possible explanations for the increased aggressiveness observed in animals receiving sesame oil (Tables 1 and 2). Studies have demonstrated that increased aggression can be associated with repeated exposure to frogs [18] or mice [10] and increased maturation [23]. The alternate day handling and injection procedure itself may have altered the aggressiveness of the control animals. Finally, the altered behavior might be related to the aminergic effects of the vehicle itself [2]. The first two of these mechanisms do not appear probable

TABLE 5

EFFECT OF TESTOSTERONE ADMINISTRATION ON WHOLE-BRAIN NOREPINEPHRINE/SEROTONIN RATIOS IN AGGRESSIVE AND NONAGGRESSIVE FEMALE RATS

	Behavior*		
Treatment	Nonaggressive	Aggressive	Combined
Sesame Oil	0.463 ± 0.010 [4]	0.545 ± 0.014 [3]	0.498 ± 0.017† [7]
Testosterone	0.535 ± 0.030 [4]	0.572 ± 0.023 [5]	0.556 ± 0.019 [9]
Combined	0.499 ± 0.020 [8]	0.562 ± 0.016‡ [8]	

*Data expressed as mean ± standard error; ratios were analyzed using ANOVA.
†$p<0.05$ Sesame vs testosterone
‡$p<0.02$ Aggressive vs nonaggressive
[ ] Number of animals/group

inasmuch as only 30 days and a single behavioral exposure occurred prior to the posthormonal (Trial 2) aggression test; nor did any of these factors effect the aggressiveness observed in control male rats previously reported [6]. Regardless of the reason for the increased aggressiveness seen in the vehicle control animals, testosterone injections failed to alter the behavior beyond that level. Furthermore, it is unlikely that a ceiling effect was reached (where an increase in aggressiveness beyond the control level is impossible) because ranacide latencies of less than 60 seconds are not unusual [4, 6, 18]. Thus, testosterone could have increased the number of killer, attackers or the speed of attack had the behavior been androgen dependent.

En toto, these behavioral results support the concept of nonandrogen dependence for ranacide behavior. Models of aggressive behavior have been classified on the basis of eliciting-stimulus [30] and the topography of the response itself [32]. Ranacide aggression can be considered a type of predatory aggression, since stimulation of the lateral hypothalamus will evoke this behavior (see [3]). Moreover as has been shown herein, the behavior appears to be nonandrogen dependent. These results support the recent hypothesis [6] that predatory aggression, as defined by the neurological model [32] is nonandrogen dependent, whereas affective aggression is androgen dependent. This model separates aggression into classes with definable neuroanatomical and neurochemical bases; thus predatory behavior can be elicited by stimulation of the ventral medial tegmentum [17] and can be enhanced pharmacologically by cholinergic stimulants or inhibited by aminergic stimulants [31]. These data are further supported by experiments utilizing synthesis inhibitors, receptor blockers or metabolic blockers [31]. Alternatively, affective aggression, the second subclass in the neurological model can be elicited by central gray matter stimulation and has pharmacological properties which are the reverse of predatory aggression. Other experiments by this author [12] suggest that shock-induced aggression may be classified as affective aggression since it is androgen dependent and has obvious autonomic components.

The biochemical findings reported herein answer several questions while raising a few new ones. Exogenous testosterone administered to either natural aggressors or nonaggressors had no effect on whole-brain levels of the indoleamine, serotonin (5-HT) or the catecholamine, dopamine (DA). Yet testosterone treated animals had significantly higher brain levels of norepinephrine than did vehicle control animals. Furthermore, this NE effect was of sufficient magnitude and uniformity across animals that analysis of the relative aminergic dominance within each animal in terms of NE/5-HT ratios, was also affected. Thus, testosterone treated rats were significantly more noradrenergic than sesame control animals which were in turn more serotonergic. The magnitude of this difference is approximately 10 percent and is similar to the difference observed between the noradrenergic aggressive animals and the serotonergic nonaggressive animals.

Several conclusions can be drawn from the above findings. First, although there were significant alterations in NE levels and NE/5-HT ratios, these changes appear to have no functional significance with regard to ranacide aggression. That is, although the brain biochemistry was altered, the aggressive behavior was not affected by testosterone treatment. Aggressive animals had relatively more NE than nonaggressive animals but this difference was not maintained following testosterone treatment. Testosterone-induced alterations in brain NE levels have been demonstrated in other studies which employed completely different measures of aggressive behavior [9,11]. In the latter study, Bernard and Paolino reported that relatively "noradrenergic" animals were aggressive in the shock-induced aggression paradigm whereas relatively "serotonergic"

animals were nonaggressive. This relationship was maintained following manipulation of testosterone levels since both the amines and aggression covaried in a similar time-dependent manner [12]. Thus, on the surface, these results indicate a possible functional role for the monoamines in shock-induced but not ranacide aggression.

At least two other interpretations of these data are possible however. First, qualitatively the changes in NE/5-HT ratios in both this study and the shock-induced aggression study were the same, while quantitatively those changes observed in the shock-induced study were much larger than that just reported. Thus, although changes observed herein reached statistical significance a greater change may be required to be of functional significance. This of course then implies the existence of some critical or minimal quantitative change in the NE/5-HT ratios which is required prior to observing a change in aggressive behavior. A second interpretation involves the mechanism of the observed changes in NE/5-HT ratios. In the shock-induced study, the lack of testosterone in male rats (castration) was associated with increased brain levels of 5-HT which was the main reason for castrates (relatively nonaggressive) having a lower NE/5-HT ratio than more aggressive animals. In the present study, the differences in monoaminergic ratios were induced by changes in NE levels, not 5-HT levels. Thus, although Tagliamonte *et al.* [37] and Bernard and Paolino [8] have suggested that changes in NE/5-HT ratios are of functional significance to behavior, this concept may be of value only when alterations in ratios are induced by changes in 5-HT, while small changes in NE have relatively little importance. These interpretations are of course speculative, however supporting evidence is available. Numerous articles have demonstrated the inhibitory effects of serotonin on predatory aggression in the rat by employing parachlorophenylalanine, a 5-HT depletor [19, 20, 28], administration of 5-hydroxytryptophan (5-HTP), a metabolic precurser of 5-HT [25] or by lesioning serotonin rich brain regions [22]. Furthermore, drugs which selectively block predatory aggression may act by increasing the activity of serotonergic neurons [34,35]. Finally, there is evidence which indicates that the serotonergic inhibitory effect is dominant compared to the possible excitatory effects of the catecholaminergic systems [26,27].

The entire brain amine-aggression hypothesis may be more complicated than indicated above. Studies employing various models of aggressive behavior have suggested that the catecholamines may play an inhibitory role with regard to some forms of aggression; these include long-term isolation induced aggression [9], septal lesion-induced hyperreactivity [7] and strain specific, age dependent changes in conspecific aggression (Bernard, Finkelstein and Everett, unpublished results). The results of the study reported herein are important from the theoretical and technical standpoint. In a previous study [11] this author demonstrated the masking effect which can be encountered when whole-brain analyses are employed. That is, considering the differential brain amine distributions, it is possible that major amine alterations within a small brain region could be hidden in whole-brain assays. This was not the case in the present study where whole-brain analyses revealed significant alterations. Although future anatomically specific studies may demonstrate regional specificity with regard to the effect of testosterone, this whole-brain analysis, together with its findings of aminergic alterations, casts doubt on the simplistic hypothesis of whole-brain amine levels or ratios being functionally related to ranacide behavior.

Several general conclusions can be drawn from this and numerous other studies. First, it is now well established that although there are some similarities across behavioral models [14,15], aggression is not a homogenous cluster of behaviors [13,24]. They are characterized by different anatomical loci, pharmacological properties and as shown above, different hormonal characteristics. Secondly, although each subclass of aggressive behaviors is associated with distinct aminergic changes, these alterations may not be generalizable across behavioral models. Several studies have in fact demonstrated differential aminergic control of ranacide, muricide and irritable aggressions [28], predatory, irritable, and spontaneous aggression, [21], or even differences within a single (irritable) aggression [36]. These findings suggest that a more fruitful approach to the study of the brain amine-affective behavior hypothesis may lie in the careful elaboration of the characteristics of the behavioral model being employed and determinations of how alterations in these basic characteristics relate to the different relationships with the brain monoamines. Theoretically, these concepts have direct applicability to the human psychiatric problem where various disease entities (models), which on the surface appear to be similar, respond in an unrelated manner to similar therapeutic manipulations of the central monoaminergic systems.

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