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Serotonin Agonist-Induced Decreases in Intermale Aggression Are Dependent on Brain Region and Receptor Subtype

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COLOGER-CLIFFORD, A., N. G. SIMON, S.-F. LU AND S. A. SMOLUK. *Serotonin agonist-induced decreases in intermale aggression are dependent on brain region and receptor subtype.* PHARMACOL BIOCHEM BEHAV **58**(2) 425–430, 1997.—Testosterone (T) and its androgenic and estrogenic metabolites modulate the ability of serotonin (5-HT)$_{1A}$ and 5-HT$_{1B}$ agonists to inhibit intermale aggressive behavior. This study tested whether the lateral septum (LS) and medial preoptic area (MPO), which are part of the neuroanatomical substrate for aggression and contain androgen, estrogen, 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors, represent sites where these modulatory effects occur. Gonadectomized CF-1 male mice were given silastic implants containing diethylstilbestrol (DES, a synthetic estrogen) or dihydrotestosterone (DHT, a nonaromatizable androgen) and implanted bilaterally with guide cannula directed at the LS or MPO. They were microinjected with either CGS12066B, a 5-HT$_{1B}$ agonist (400 μM LS, 200 μM MPO); 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), a 5-HT$_{1A}$ agonist (10 μM LS, 5 μM MPO); or combined CGS + 8-OH-DPAT treatment and tested for aggression 15 min later. When microinjections were given in the LS, androgen-treated males exhibited significantly reduced attack behavior in response to CGS or to CGS + 8-OH-DPAT. The attack behavior of DES-treated males was not reduced by any of the treatments. In contrast, all agonist treatments decreased aggression when injected into the MPO in both hormone conditions. The findings demonstrate regional variation in the ability of androgens and estrogens to modulate 5-HT$_{1A}$- and 5-HT$_{1B}$-agonist mediated reductions in aggression. © 1997 Elsevier Science Inc.

Testosterone Androgen Estrogen Serotonin 8-OH-DPAT CGS Aggression Mice

THE DISPLAY of offensive aggression is facilitated by testosterone (T) (2,11,21). Subsequent castration-replacement studies in male mice have refined this position to reflect distinct pathways regulated by the estrogenic and androgenic metabolites of T, with the functional system determined by genotype. For instance, CF-1 males exhibit aggression in response to androgenic or estrogenic stimulation, the CFW strain responds to estrogens and the CD-1 strain primarily to androgens (54,56,57). In parallel with this research is substantial pharmacological evidence supporting an inhibitory role for the neurotransmitter serotonin in the regulation of aggression (15,28,33,35,43). Findings with selective receptor agonists and genetically engineered mice have strongly indicated that the serotonergic effects are mediated through the serotonin (5-HT)$_{1A}$ and/or 5-HT$_{1B}$ receptors subtypes (6,23,35, 42,43,49).

A recent study has demonstrated an interaction between these neuroendocrine and neurochemical systems (16), with the hormonal environment determining whether systemically administered serotonergic agonists can attenuate aggression. In the presence of nonaromatizable androgen, 5-HT$_{1A}$, 5-HT$_{1B}$ and combined agonist treatments reduced aggression. In the presence of estrogen or T, the latter of which provides both estrogenic and androgenic stimulation, only 5-HT$_{1A}$ and 5-HT$_{1A}$ + 5-HT$_{1B}$ treatments decreased aggression, whereas the 5-HT$_{1B}$ agonist given alone had no behavioral effect.

These observations suggested that a potential mechanism through which steroids facilitate aggression may be through alterations in 5-HT function in regions that have been implicated in the regulation of this behavior, are targets for androgen and estrogen, and also exhibit 5-HT$_{1A}$ and/or 5-HT$_{1B}$ receptor sites. Two such regions are the lateral septum (LS) and

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medial preoptic area (MPO). Lesion studies have shown that ablation of these areas significantly reduce or eliminate aggression in rats and mice (1,8,27,58). Further, steroid implants in castrated males in both the MPO and LS generally increase the expression of fighting behavior (4,5,44), although some groups have failed to observe such effects (29,41). Both immunochemical and autoradiographic studies have demonstrated the presence of androgen and estrogen receptors in these areas (25,30,48,50,54,60), and autoradiographic distribution maps of 5-HT_{1A} and 5-HT_{1B} receptors have demonstrated moderate-to-high levels of these subtypes in LS and MPO (12,13,22,26,37,45,46). Although direct investigations of the role of LS and MPO in serotonergic modulation of aggression are few in number, these regions bind [^{3}H]eltoprazine (ELT), a combined 5-$HT_{1A/1B}$ agonist that inhibits offensive aggression (51). Enhanced sensitivity to the antiaggressive effect of ELT following 5,7-DHT lesions to serotonergic neurons originating from the dorsal and median raphe has been associated with increased 5-HT_{1A} binding in the LS and increased 5-HT_{1B} binding in the MPO. In addition, intraventricular injections of TFMPP, a nonselective 5-HT_{1B} agonist, reduced aggression in male rats (38). The presumed mechanism, at least in part, involved drug diffusion into surrounding structures including LS, thus providing additional support for the involvement of 5-HT_1B receptors in this region in aggression.

These findings indicate that the LS and MPO may be major sites for steroidal modulation of 5-HT function in the regulation of male-typical offensive aggressive behavior. To test this concept, gonadectomized males were implanted with specifically acting androgens or estrogens, microinjected with 5-HT_{1A}, 5-HT_{1B} or combined 5-$HT_{1A/1B}$ agonists in LS or MPO and then were tested for aggression. The results demonstrated regional variation in hormonal modulation of drug effects and suggest potential refinements in the neuroanatomy of intermale aggression.

METHOD

Animals

CF-1 male mice, 50–60 days of age, were purchased from the Charles River Breeding Farm (Wilmington, MA). This strain was selected because it expresses both neuroendocrine pathways for aggression, thus allowing independent assessments of androgenic and estrogenic effects on serotonin agonist function. The mice were group housed in 28- × 18- × 13-cm polypropylene cages lined with wood shavings. Food and water were provided in excess and the colony was maintained at 22 ± 2°C, with a 12:12-h light:dark cycle with lights on at 0800 h. All procedures complied fully with Federal guidelines for the care and treatment of animals.

After a 1-week adaptation period, males were castrated and returned to group housing. Two weeks later, each male mouse was housed with a female mouse and was screened 48 hrs later for biting attacks toward an olfactory bulbectomized male. Females were removed prior to testing. Males that did not show biting attacks (>80%) were then implanted subcutaneously with a 10-mm length of silastic tubing (inner diameter = 0.062 in) containing either the synthetic estrogen diethylstibestrol (DES; 0.5 mg/0.02 cc) or the nonaromatizable androgen dihydrotestosterone (DHT; 5.0 mg/0.02 cc) and were rehoused with a female. The hormonal treatments were selected for their specificity and behavioral efficacy. Diethylstilbestrol, in contrast to estradiol, does not cross react with androgen receptor (14,18,54), and DHT, which is nonaromatizable [e.g., (32)], provides only direct androgenic stimulation. Behaviorally, specific estrogenic and androgenic treatments restore aggression in castrated CF-1 males to a level comparable to that seen in intact or gonadectomized T-treated males (54).

Two weeks after receiving the silastic implant, males were again screened for biting attacks against an olfactory bulbectomized male intruder. Only those males that showed at least five biting attacks, i.e., those that met an established criteria for aggression [e.g., (53,55)], were used in the experiments.

Cannula Implantation

Males were anesthetized with sodium pentabarbitol (Nembutal) and placed in a Kopf stereotaxic apparatus fitted with a mouse head holder. Bilateral 26-guage cannulae were implanted to a depth of 1 mm above the injection sites according to coordinates in Slotnick and Leonard (59) for the LS (AP = +0.4, DV = −2.2, and L = 0.6) and MPO (AP = +0.1, DV = −4.2, and L = 0.2). The cannulae were held in place with acrylic dental cement, and cyanoacrylate adhesive was used to seal the skin. A stainless steel stylet was placed in each cannula to insure patency.

Drug Microinjections

One week following surgery, animals were rescreened for aggression. Those that fought (about 75% within each hormone treatment) were randomly divided among the following groups. Animals with LS implants were microinjected with (a) CGS 400 μm, the most selective 5-HT_{1B} agonist currently available (40); (b) 8-OH-DPAT 10 μM, a highly selective 5-HT_{1A} agonist (3,24,36); (c) CGS 400 μM + 8-OH-DPAT 10 μM; or (d) water vehicle. Animals with MPO implants received (a) CGS 200 μM, (b) 8-OH-DPAT 5 μM, (c) CGS 200 μM + 8-OH-DPAT 5 μM or (d) water vehicle. The dosages were based on pilot data that showed that LS microinjections at these concentrations altered aggression without effecting motor function. The MPO concentrations were reduced by 50% because sedation was observed with 400 μM CGS and 10 μM 8-OH-DPAT. Drugs were purchased from Research Biochemicals, Inc. (Natick, MA) and were administered bilaterally using a 5-μl syringe connected with silastic tubing to a 33-gauge glass tube cut to extend 1 mm beyond the cannula tip. Drugs were dissolved in distilled water and injected in a volume of 0.1 μl. Animals were held by hand during the procedure, and the glass tubing remained fully inserted in the cannula for 60 s postinjection. Testing began 15 min later.

Behavioral Tests

Tests for aggression took place in the home cage of the experimental male. The female was removed, and an olfactory bulbectomized CF-1 stimulus male, of comparable weight and age, was introduced into the home cage. Olfactory bulbectomized males were used because, although they elicit aggression, they do not fight back (17). Therefore, any aggression displayed can be reliably ascribed to the experimental male. Preliminary screening tests lasted for a maximum of 10 min or until 5 biting attacks were exhibited by the experimental male. Under drug treatment conditions, tests were videotaped for 15 min following the introduction of the stimulus male. Scoring began 5 min into the session to allow for habituation and then continued for 10 min. The following behaviors were recorded for each experimental male: anogenital sniffing, rough grooming, lateral threat, tail rattling and biting attack, which are associated with aggression (10), and locomotion and rearing as indices of motor behavior.

Histology

Males were perfused with saline followed by 4% paraformaldehyde. The brains were removed and postfixed in 4% paraformadehyde. Twelve hours before sectioning, brains were transferred to a 10% sucrose solution. Brains were sectioned (40 μm) on a cryostat and mounted on gelatin-coated slides. Sections were stained with cresyl violet and accuracy of cannula placement was verified by microscopic examination.

Data Analysis

Data were analyzed using a series of one-way analyses of variance that compared the effects of the drugs in the presence of each steroid. Planned comparisons were conducted for each drug vs. the water control. Aggression was measured as the combined frequency of biting attacks, lateral threats and tail rattling (52). Anogenital sniffing and rough grooming were rarely shown by the experimental males during the 10-min recording period and therefore were not included in the analyses. Motor behavior was measured by combining the frequency of locomotion (grid crossings) and rearing.

RESULTS

Findings with LS microinjections are shown in Fig. 1. In the presence of DES, there were no significant overall effects of 8-OH-DPAT, CGS or 8-OH-DPAT + CGS injections on aggression or motor behavior. In contrast, in the presence of DHT, significant effects on aggression were found [$F(3, 23) = 3.01$, $p < 0.05$]. Microinjections of CGS given alone [$t(1) = 5.18$, $p < 0.05$] or in combination with 8-OH-DPAT [$t(1) = 9.34$, $p < 0.05$] reduced the frequency of offensive behaviors in comparison with controls without significant changes in motor function. The 8-OH-DPAT given alone did not effect either behavior.

Microinjections into the MPO produced a different pattern of results (Fig. 2). In this region, there were significant overall effects on aggression in both DES-treated [$F(3, 25) = 5.09$, $p < 0.05$] and DHT-treated [$F(3, 26) = 3.16$, $p < 0.05$] males. In the DES condition, all agonist treatments significantly decreased aggression in comparison with controls [CGS: $t(1) = 10.23$; 8-OH-DPAT: $t(1) = 4.40$; CGS + 8-OH-DPAT: $t(1) = 10.61$; all ps < 0.05]. Significant effects on motor behavior were observed [$F(3, 25) = 3.87$, $p < 0.05$], but planned comparisons revealed that this effect was limited to the 8-OH-DPAT + CGS group [$t(1) = 9.68$, $p < 0.05$; all other comparisons vs. controls were not significant]. In the presence of DHT, 8-OH-DPAT [$t(1) = 5.08$, $p < 0.05$] and CGS [$t(1) = 8.58$, $p < 0.05$] significantly reduced aggression, whereas the combined treatment produced a marginal reduction [$t(1) = 4.05$, $p = 0.055$]. None of the drugs significantly altered motor behavior in DHT-implanted males.

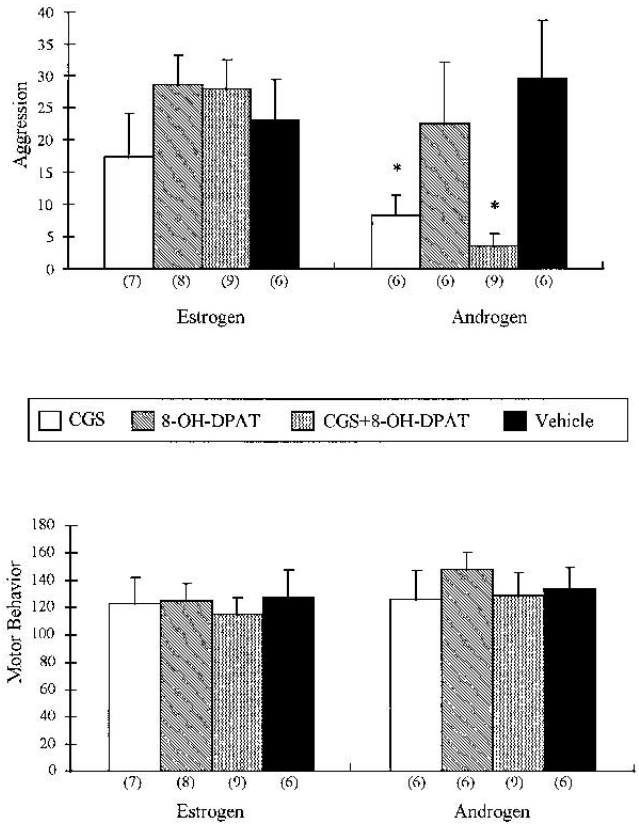

FIG. 1. Effects of microinjections of 5-HT_{1A} (8-OH-DPAT) and 5-HT_{1B} (CGS12066B) agonists into the LS of CF-1 male mice treated with either DES (estrogen) or DHT (androgen). Aggression scores are expressed as the mean ± SEM of biting attacks + lateral threats + tail rattling. Motor behavior represents the mean ± SEM of locomotion + rearing. The number of mice in each condition is shown in parentheses. *Significantly different from water vehicle ($p < 0.05$).

DISCUSSION

The demonstration of regional differences in estrogenic and androgenic effects on 5-HT_{1A} and 5-HT_{1B} agonist function represents the major finding of this study. In the presence of estrogens, 8-OH-DPAT and CGS attenuated aggression when injected into the MPO but had no effect at the level of the LS. In the presence of androgen, both drugs again effectively inhibited aggression in the MPO, whereas CGS but not 8-OH-DPAT reduced fighting behavior when microinjected into the LS. These observations extend previous work that described hormonal modulation of the aggression-attenuating effects of systemically administered 5-HT_{1A} and 5-HT_{1B} agonists (16). In addition, the findings suggest refinements in our understanding of the neuroanatomical circuitry underlying T-dependent, offensive aggression.

Regional differences in the aggression-attenuating effects of 5-HT_{1A} and 5-HT_{1B} agonists have been reported previously (38,39). The 8-OH-DPAT microinjection into the dorsal raphe (DR) decreased aggression in male rats but had no effect when injected into the lateral ventricle. Conversely, intraventricular injection of the putative 5-HT_{1B} agonist TFMPP reduced aggression but had no effect in the DR. Atlhough the potentially different roles of pre- vs. postsynatpic 5-HT receptors in the regulation of aggression can account for these findings, it cannot explain the differences obtained between the LS and MPO microinjections because autoradiographic and chemical lesion studies have shown that both subtypes are primarily localized postsynaptically in these regions (20,31, 37,51). Thus, a critical question involves the identification of potential mechanisms through which estrogens and androgens contribute to the differences in agonist function between the LS and MPO.

Gonadal steroids can effect a range of processes that potentially influence the action of 5-HT, including receptor density, the affinity of ligand–receptor interactions, turnover rate,

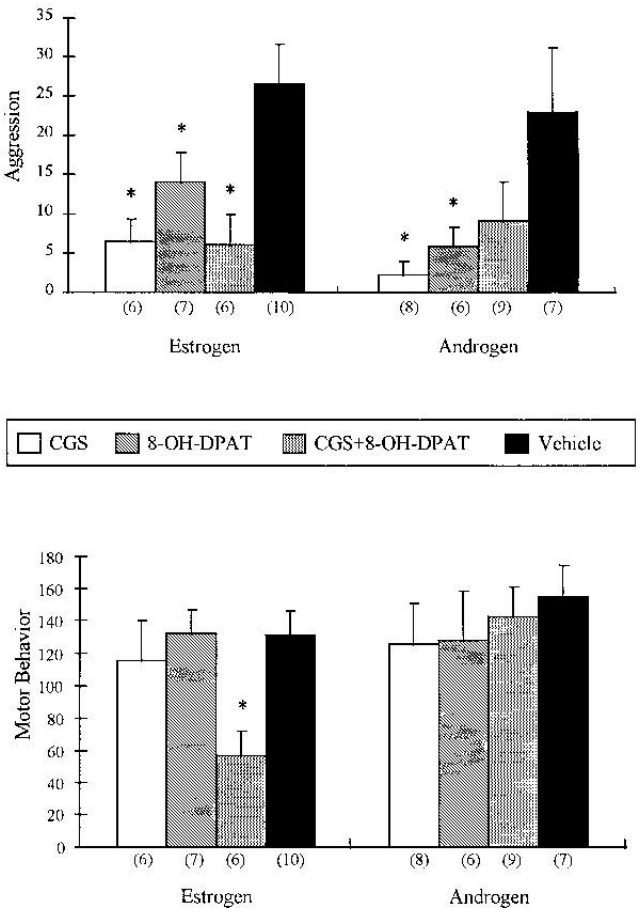

FIG. 2. Effects of microinjections of 5-HT_{1A} (8-OH-DPAT) and 5-HT_{1B} (CGS12066B) agonists into the MPO of CF-1 male mice treated with either DES (estrogen) or DHT (androgen). Aggression scores are expressed as the mean ± SEM of biting attacks + lateral threats + tail rattling. Motor behavior represents the mean ± SEM of locomotion + rearing. The number of mice in each condition is shown in parentheses. *Significantly different from water vehicle ($p < 0.05$).

synthesis and/or transporter function. Although few studies have directly addressed these relationships in the context of male-typical behavior, androgen- and estrogen-induced changes in 5-HT receptor binding and turnover rates have been the subject of a few investigations. In the LS, for example, castration of male rats decreased [^{3}H]5-HT binding (19). This decrease was not reversed by estradiol benzoate (EB), indicating a direct androgenic effect on receptor levels. In MPO, castration reduced [^{3}H]8-OH-DPAT binding in males, whereas T returned 5-HT_{1A} receptor density to normal levels (20,34), supporting the concept of androgenic regulation of 5-HT_{1A} receptors. The 5-HT_{1B} density, in contrast, was not altered in MPO by gonadectomy (20). Regarding hormonal effects on 5-HT or 5-HIAA levels, results have been inconsistent. Castration reportedly decreased both septal and hypothalamic 5-HT in rats after extended isolation (47). Bitar et al. (7) also reported decreased 5-HT and increased 5-HIAA in the hypothalamus following castration, with levels returned to those of intact animals by EB but not TP. In contrast, castration increased 5-HT in the anterior and ventromedial nuclei of the hypothalamus, with TP restoring 5-HT to intact levels (61). There were no effects of castration or steroid treatment on 5-HT levels in the MPO. Bradshaw et al. (9) reported no effects of castration or subcutaneous implants of T, DHT, E_2, or E_2 + DHT on 5-HT or 5-HIAA concentrations in these same hypothalamic nuclei and in the MPO. Some of the variation among these studies may be accounted for by methodological differences. For instance, castration of individually housed males decreased 5-HT in the hypothalamus (7,47), but it had no effect on group housed animals (9), suggesting that housing condition may affect steroidal modulation of 5-HT levels. In addition, differences in the duration of steroid treatment and the interval between castration and 5-HT assay (45 vs. 30 vs. 7 days) also could have potentially contributed to the discrepant results. Nevertheless, these findings, combined with the binding studies, tentatively suggest that in males androgens may act on 5-HT receptor density and that both androgens and estrogens influence 5-HT metabolism. It appears premature, however, to speculate about the relationship between these mechanisms and the present results because of the paucity of data, disparities among the 5-HT metabolism studies, and the fact that none of the studies utilized mice.

The present findings enhance models of the neuroanatomical substrates regulating intermale aggression. At the level of the LS, androgen–5-HT_{1B} agonist interactions were the most important. Estrogen–5-HT_{1B} interactions or 5-HT_{1A} activity in the presence of either steroid had no effect on aggression. One possibility is that the inability of 8-OH-DPAT to attenuate aggression may have been because the dose was too low. However, this seems unlikely because microinjections of a lower dose (5 μM) in the MPO, which is a region with lower 5-HT_{1A} receptor levels (45,46), significantly reduced fighting behavior. Alternatively, 5-HT_{1A} receptors in the LS may not play a regulatory role in either estrogen- or androgen-dependent aggression. Support for LS 5-HT_{1B} but not for 5-HT_{1A} receptors in aggression also was suggested by a previous report demonstrating that intraventricular injection of TFMPP but not 8-OH-DPAT decreased aggression in part through its diffusion into the surrounding LS (38). Further, the effects of 5-HT_{1B} agonist microinjections into LS were consistent with the systemic effects of CGS in an earlier study, where it reduced aggression in the presence of androgens but not estrogens (16). Together, these findings suggest that the LS may be primarily part of an androgen-dependent regulatory pathway that is modulated by 5-HT_{1B} receptor function in this region. Regarding the MPO, both 5-HT_{1A} and 5-HT_{1B} agonists given alone attenuated aggression in the presence of either steroid. Combined agonist treatments also reduced aggression, although the motor effects observed in estrogen-treated males suggest some caution in regard to this finding. Overall, these results indicate that the MPO is part of both the androgen-dependent and estrogen-dependent circuits regulating aggression and that it is a locus of T–5-HT interactions in relation to this behavior.

In general, the results refined the role of the LS and MPO in offensive aggression by demonstrating variation in the ability of 5-HT_{1A} and 5-HT_{1B} agonists to attenuate aggression based on the site and the steroidal environment. At the level of the LS, significant effects on aggression were produced only by CGS and CGS + 8-OH-DPAT in androgen-treated males. The 5-HT_{1B} agonist had no effect in estrogen-treated animals and 8-OH-DPAT given alone did not reduce aggression in the presence of either steroid. These findings suggest that steroids differentially affect 5-HT_{1B} activity in the LS and that 5-HT_{1A} receptors in this region may not be involved

in the inhibition of offensive aggression. In contrast, 8-OH-DPAT and CGS injections into the MPO decreased aggression in the presence of both steroids, indicating that 5-HT_{1A} and 5-HT_{1B} function at this level are part of the regulatory pathway for both estrogen- and androgen-mediated aggression.

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