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Evolutionary Changes in Dopaminergic Modulation of Courtship Behavior in *Cnemidophorus* Whiptail Lizards

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Preoptic dopamine release is integral to the display of copulatory behaviors in male mammals and birds. However, while the anatomical distributions of the dopamine synthesizing enzyme tyrosine hydroxylase are similar among vertebrates, evolutionary changes in the functional role of dopamine are poorly understood. In this study, we tested whether a dopamine D1 receptor agonist would facilitate the display of courtship and copulatory behaviors in two related *Cnemidophorine* lizards (*Cnemidophorus inornatus* and *Cnemidophorus uniparens*). *Cnemidophorus* lizards offer a unique system to study evolutionary changes in functionality because ancestral (e.g., *C. inornatus*) and descendant (e.g., *C. uniparens*) species can be studied in parallel. *Cnemidophorus uniparens* is an all-female, parthenogenetic species and is the triploid descendant of the sexual and diploid species *C. inornatus.* Here we report that in castrated male *C. inornatus* and ovariectomized *C. uniparens* a dopamine D1 agonist increased the proportion of individuals mounting and decreased the latency to mount. Moreover, there was a species difference in sensitivity to the agonist: Mounting was elicited at a lower dose in *C. uniparens* than in *C. inornatus.* One possible explanation for this heightened sensitivity in the triploid parthenogen is that, by virtue of the increased ploidy, the parthenogen has elevated levels of D1 receptor in limbic brain areas modulating courtship behavior.

Key Words: **dopamine; courtship; ploidy; lizard; SKF 81297.**

The neurotransmitter dopamine (DA) has been implicated in the regulation of male copulatory behaviors in rodents (reviewed in Melis and Argiolas, 1995). Studies on the role of DA in modulating sexual behaviors have focused on the mesolimbic system, mainly on projections from the A10 cell bodies in the ventral tegmental area to the nucleus accumbens, and the incertohypothalamic system (A12–A15), which sends projections into the hypothalamus and preoptic area (Moore and Lookingland, 1995). Dopamine transmission increases in both the nucleus accumbens (Damsma, Pfaus, Wenkstern, Phillips, and Fibiger, 1992; Mas, Fumero, and Gonzalez-Mora, 1995; Mas, Gonzalez-Mora, Louilot, Sole, and Guadalupe, 1990; Pfaus, Damsma, Nomikos, Wenkstern, Blaha, Phillips, and Fibiger, 1990; Pfaus and Phillips, 1991) and the medial preoptic area (Hull, Du, Lorrain, and Matuszewich, 1995) when males are presented with a sexually receptive female as well as when males engage in copulation. The rate, efficiency, and probability of copulatory behavior is affected both by peripheral injections and by microinjections into the medial preoptic area of DA agonists and antagonists (Bignami, 1966; Butcher, Butcher, and Larson, 1969; Hull, Bitran, Warner, Band, and Holmes, 1986; Bitran and Hull, 1987; Warner, Thompson, Markowski, Loucks, Bazzett, Eaton, and Hull, 1991; Hull, Eaton, Markowski, Moses, Lumley, and Loucks, 1992; Markowski, Eaton, Lumley, Moses, and Hull, 1994).

There are five DA receptor subtypes that can be categorized into two types (D1 and D2) based on pharmacology and second messenger systems (Neve and Neve, 1997). In rodents, D1 and D2 receptor types affect different components of male sexual behavior: D1-type receptor activation facilitates the early stages of copulation while D2-type receptor activation facil-

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itates ejaculation (Moses, Loucks, Watson, Matuszewich, and Hull, 1995).

The only nonmammalian species in which the role of DA in copulatory behavior has been studied is the Japanese quail. As in rats (Hull, Du, Lorrain, and Matuszewich, 1997), D1 receptor activation facilitates, while D2 receptor activation inhibits, preejaculatory aspects of copulatory behavior (e.g., mount attempts) in the male quail (Balthazart, Castagna, and Ball, 1997). Furthermore, there are a number of similarities in the distribution of tyrosine hydroxylase (TH), the DA synthesizing enzyme, between quail and rats. For example, in quail, incertohypothalamic DA cells project into the medial preoptic nucleus, an area critical for the expression sexual behaviors (Bailhache and Balthazart, 1993). In summary, responses to dopaminergic drugs and neuroanatomical distribution of TH are similar between quail and rodents.

Research on DA in reptiles has thus far focused only on the distribution of TH, while the role of DA in sexual behaviors in reptiles is largely unknown. There are a number of dopaminergic nuclei that are potentially homologous to those in mammals. For example, in *Gekko gekko* TH-immunoreactive (TH-IR) cells in the ventral tegmental area project to the nucleus accumbens, and TH-IR cell bodies in both the periventricular preoptic area and the paraventricular hypothalamus send projections into the anterior hypothalamus and preoptic area (reviewed in Smeets, 1994). However, relatively little is known about whether anatomical similarity or homology in neurotransmitter systems across vertebrates is correlated with similarity in function. The comparison between rats and quail suggests that this is the case. We hypothesized that because of the substantial conservation in the role of preoptic, hypothalamic, and amygdalar nuclei in the control of sexual behaviors (Crews and Silver, 1985; Meisel and Sachs, 1994), similarities in neurochemical distribution are likely to be correlated with similarities in neurochemical function.

In this experiment we assessed the behavioral effects of the full, specific D1 receptor agonist SKF 81297 on courtship behavior in *Cnemidophorus inornatus* males and *Cnemidophorus uniparens* individuals. Whiptail lizards (genus *Cnemidophorus*) represent a unique system to investigate the evolution of neural foundations of sexual behavior. Approximately one-third of the species in the genus are parthenogenetic, or all-female, as a result of hybridization events and are direct descendents of extant, sexually reproducing species. In many of the parthenogenetic species, individuals reliably and consistently display both male- and female-typical sexual behaviors (Crews, 1989). *Cnemidophorus uniparens* is a triploid, unisexual species that arose from two hybridization events, both putatively involving males of the diploid sexual species *C. inornatus* (Wright, 1993). Therefore, through comparisons between these two species, we can directly assess how the brain changed due to this evolutionary transition and how changes in ploidy can affect brain–behavior relationships. We predicted that the D1 agonist would increase the display of copulatory behavior in both species. Furthermore, given previous work that has found differences in sensitivity between the two species in response to steroid hormones, we also predicted that there would be species differences in the sensitivity to the agonist due to ploidy. That is, we hypothesized that *C. uniparens* individuals would require a lower dose of the agonist to induce courtship behavior.

METHODS

Lizards were captured either in Portal, Arizona (*C. uniparens*), and housed in groups of four or five in large aquaria (78 × 29 × 29 cm) or were captured in Sanderson, Texas (*C. inornatus*), and housed individually in aquaria divided into compartments (26 × 29 × 29 cm). Throughout the experiment animals were maintained in environmental chambers under breeding conditions as described previously (Wade and Crews, 1991). They were fed three to five crickets or mealworms three times a week and had water *ad libitum*.

Cnemidophorus uniparens

Shortly after arriving in the laboratory from the field (Portal, AZ), 37 group-housed *C. uniparens* were ovariectomized under cold anesthesia as described in Wade and Crews (1991) and housed in isolation (26 × 29 × 29 cm). One week after surgery, individuals were injected intraperitoneally with 0.5 μg of estradiol benzoate (EB) in steroid suspension vehicle. This injection was given so as to mimic the preovulatory estrogen surge, which is postulated to prime the display of pseudocopulatory behavior (Godwin and Crews, 1999). Forty-eight hours later, individuals received an intraperitoneal injection of 0.005 (n = 8), 0.05 (n = 6), or 0.5 (n = 12) μg/kg of the full, specific D1 receptor agonist SKF 81297 (hereafter SKF) or vehicle (water; n = 11). All doses were prepared immediately prior to injection. Beginning 15 min after the injection

we tested experimental individuals in their home cage for 1 h with a sexually receptive stimulus *C. uniparens.*

Cnemidophorus inornatus

Forty sexually active *C. inornatus* males were castrated under cold anesthesia after screening for sexual vigor. Males that mounted females on at least 3 of 5 consecutive tests while gonadally intact were considered sexually active. After castration, we tested individuals for the loss of courtship behaviors and then implanted them with a Silastic implant (10 mm in length, 1.47 mm inner diameter, 1.96 mm outer diameter) containing progesterone (P) to determine each individuals capacity to display courtship behavior with P implants (i.e., P-sensitivity). Beginning 3 days after implantation, males were given 20 consecutive tests with a receptive female. Individuals were considered P-sensitive if they courted on at least 3 of 5 tests (floating tally) during the 20 daily tests following P implantation. Only P-sensitive males were used in this study because P-sensitive males are putatively involved in the hybridization processes leading to *C. uniparens* (reviewed in Crews and Sakata, 2000). After P-sensitivity screening, implants were removed, and beginning the following day males were screened for the loss of sexual behavior. Ten daily tests were administered, and only males that failed to court on at least 5 consecutive tests were used in this study. Thus, all males in this study were P-sensitive, but sexually inactive when given the DA manipulation. Males were injected intraperitoneally with 0.005 ($n = 6$), 0.05 ($n = 8$), or 0.5 ($n = 7$) μg/kg of SKF or vehicle ($n = 6$) 15 min prior to a 1-h behavior test with a sexually receptive *C. inornatus* stimulus female.

Testing of individuals of both species occurred in the individual's home cage under heat lamps between 10:00 and 15:00, when animals are most active. Receptivity was induced in the stimulus animals of both species using 0.5 μg of EB injected 24 h prior to testing. Stimulus animals of both species were screened for receptivity prior to testing with either a sexually experienced, testosterone-implanted *C. inornatus* male or *C. uniparens* individual. In all of the tests, we recorded the latency to the first approach, mount, and neckgrip. The sequence of courtship behaviors has been described in detail in Lindzey and Crews (1986). Briefly, individuals approach, then mount, then grip the stimulus animal's neck with their jaws while rapidly undulating their pelvis laterally on top of the stimulus animal (termed neck grip). After 1 to 3 min of remaining mounted on the female individuals will intromit the stimulus female. In this study, mounts were recorded only when individuals remained straddling the stimulus animal for at least 3 s. For each measure, if an individual failed to perform that particular behavior the maximum latency score (3600 s) was recorded.

The research presented here was approved by the Institute for Animal Care and Use Committee of the University of Texas at Austin and adhered to the National Institute of Health *Guide for the Care and Use of Laboratory Animals.*

Statistical Analyses

All analyses of the effects of dose were done within each species. The latencies to approach, mount, and neckgrip as well as the interval between approach and mount were analyzed using a nonparametric Kruskal–Wallis test because of heteroscedasticity in the data. Dose was the sole independent variable. When there was an overall effect of DA treatment, each dose was compared to the vehicle control using Wilcoxon rank-sum tests. Likelihood Ratio tests were used to analyze the percentage of individuals courting at each dose. Finally, to analyze species differences, the latencies to approach and mount were compared between *C. inornatus* and *C. uniparens* given the effective dose using Wilcoxon rank-sum tests. Likewise, the percentage of individuals mounting in each species with the effective dose was analyzed with a likelihood ratio test. Significance was determined at an α level of 0.05.

RESULTS

Cnemidophorus uniparens

There was no significant effect of SKF on approach latencies in *C. uniparens,* suggesting that there were no robust motor side effects of the drug. However, SKF increased the display of mounting behavior. There was an overall effect of SKF on the absolute latency to mount ($\chi^2_3 = 12.405$, $P = 0.006$) as well as on the interval between first approach and first mount ($\chi^2_3 = 12.405$, $P = 0.006$). Post hoc tests revealed that treatment with 0.005 μg/kg (effective dose) of SKF decreased the absolute latency to mount ($Z = -2.489$, $P = 0.013$) as well as the interval between the first approach and the first mount ($Z = -2.489$, $P = 0.013$; Fig. 1) relative to individuals treated with vehicle. Other doses of SKF were ineffective at decreasing mount latencies. Likewise, the effective dose of

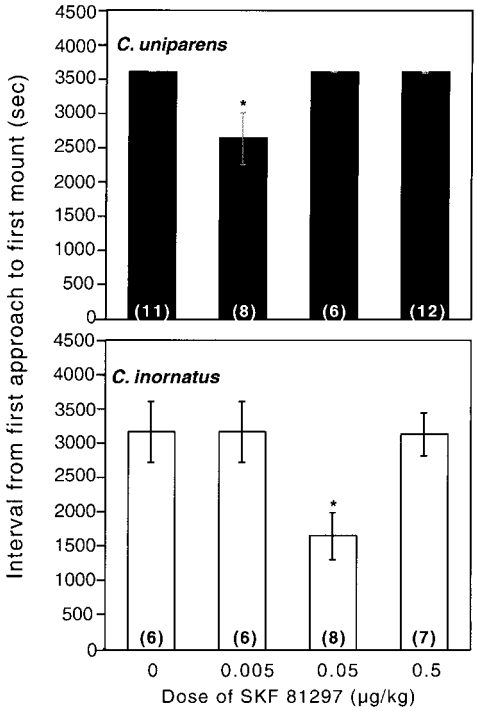

FIG. 1. Effects of the full, D1 receptor agonist SKF 81297 on the interval between the first approach and first mount in two related species of whiptail lizard: the ancestral *C. inornatus* and the descendent species *C. uniparens.* The asterisk indicates that the treatment significantly decreased the interval from approach to mount relative to vehicle-treated individuals at $\alpha < 0.05$.

SKF increased the proportion of individuals mounting relative to treatment with vehicle ($\chi^2_3 = 8.466$, $P = 0.004$; Fig. 2) while the other doses had no effect on the proportion of animals mounting. There was no significant effect of treatment on neck grip latencies.

Cnemidophorus inornatus

The latency to approach was not affected by SKF in *C. inornatus.* There was an overall effect of SKF on the absolute latency to mount ($\chi^2_3 = 10.279$, $P = 0.016$) as well as the interval between first approach and first mount ($\chi^2_3 = 10.581$, $P = 0.014$; Fig. 1). Post hoc tests revealed that, relative to vehicle injections, treatment with 0.05 μg/kg of SKF (effective dose) decreased the latency to mount ($Z = 2.284$, $P = 0.022$) as well as the interval from first approach to first mount ($Z = 2.150$, $P = 0.032$). The other doses of SKF did not significantly affect mount latencies. The dose of 0.05 μg/kg (effective dose) also increased the proportion of individuals mounting relative to vehicle treatment ($\chi^2_1 = 7.686$, $P = 0.006$). Treatment with SKF did not affect neckgrip latencies.

To assess qualitative differences in courtship behaviors elicited by the D1 agonist, we compared the responses of both species at their effective doses (i.e., 0.005 μg/kg for the parthenogen and 0.05 μg/kg for *C. inornatus*). Approach, mount, and neckgrip latencies were not significantly different between the species at the effective doses. However, there was a trend for the interval from first approach to first mount to be shorter in *C. inornatus* males than in *C. uniparens* ($Z = 1.652$, $P = 0.099$; Fig. 1) and a trend toward a higher proportion of *C. inornatus* males mounting relative to *C. uniparens* individuals ($\chi^2_1 = 2.756$, $P = 0.097$; Fig. 2).

DISCUSSION

In this study, we found that the D1 agonist SKF 81297 increased the display of mounting behavior in two related species of lizard: *C. inornatus,* the ances-

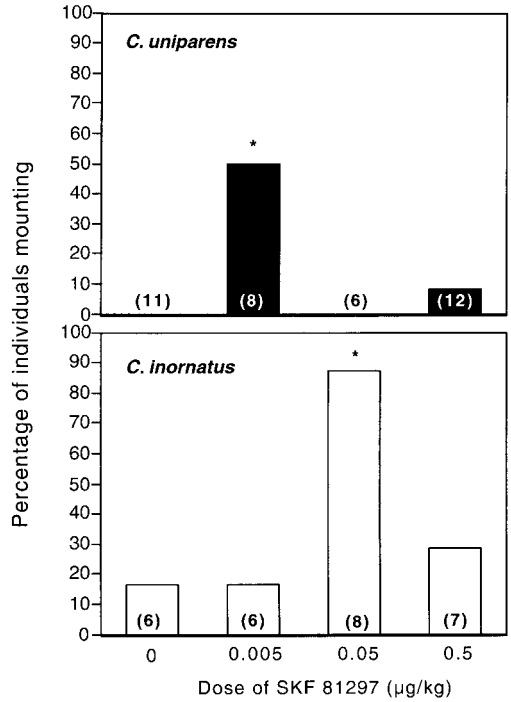

FIG. 2. Effects of the full, D1 receptor agonist SKF 81297 on percentage of individuals mounting in two related species of whiptail lizard: the ancestral *C. inornatus* and the descendent species *C. uniparens.* The asterisk indicates significantly more individuals mounting in that treatment group relative to vehicle-treated individuals ($P < 0.05$).

tral, diploid species, and *C. uniparens*, the descendant, triploid species. This is the first experiment, to our knowledge, that demonstrates an effect of DA on courtship behavior in lizards. We found that SKF elicited mounting at a lower dose in *C. uniparens* than in *C. inornatus*. The species also differed in the robustness of their response to SKF, although these differences did not reach significance: Overall, a greater percentage of *C. inornatus* males mounted and mounted sooner than did *C. uniparens* individuals given the effective dose. The increase in the display of courtship behaviors in response to a D1 agonist in these species indicates that DA is also significant in the control of sexual behaviors in lizards. Further, the behavioral responses support the hypothesis that similar distributions of dopaminergic cells between mammals, birds, and reptiles may have similar functions across taxa.

Of particular interest is the finding that the parthenogen required a lower dose of SKF to display mounting behavior than male *C. inornatus*. *Cnemidophorus uniparens* individuals are triploid hybrids, and it is speculated that two-thirds of their genome comes from *C. inornatus* (Wright, 1993). Previous work has found that they express higher levels of estrogen receptor (ER) and progesterone receptor (PR) mRNA in hypothalamic and preoptic regions than do either males or females of the ancestral species (Godwin and Crews, 1995; Young, Nag, and Crews, 1995a,b). Further, *C. uniparens* are more sensitive to the effects of estrogen on receptive behavior than are *C. inornatus* females: A lower dose of estrogen is required in *C. uniparens* to induce receptivity. It is hypothesized that this heightened sensitivity is due to elevated levels of ER in the parthenogen and that this is directly related to the addition of a third copy of the genome. We propose that the increase in ploidy in *C. uniparens* accounts for the difference in sensitivity to SKF and that D1 receptor expression may be elevated in areas like the preoptic area and nucleus accumbens in *C. uniparens*.

On the other hand, it is possible that the species difference is due to differences in experimental design between the species. For example, that *C. uniparens* individuals were group-housed prior to ovariectomy, whereas *C. inornatus* males were always housed in isolation, could have contributed to the heightened sensitivity of the parthenogen. Furthermore, a priming dose of estrogen was administered to *C. uniparens* but not to *C. inornatus* males 48 h before the tests with SKF. It is possible that the estrogen injection up-regulated D1 expression in preoptic and hypothalamic areas as has been found in cell cultures (Lee and Mouradian, 1999). However, estrogenic stimulation may not be critical in the dopaminergic modulation of masculine behavior, as male ERα knock-out mice do not differ from wild-type males in their reactivity to apomorphine (Wersinger and Rissman, 2000).

The difference in DA sensitivity may also be due to the fact that *C. inornatus* males and *C. uniparens* individuals are of different sexes. In rats, males have fewer TH-IR cells in an area of the periventricular preoptic area (pvPOA) than do females (Simerly, Swanson, Handa, and Gorski, 1985). The pvPOA has been implicated in the evolution of male-typical pseudocopulatory behavior in *C. uniparens* (Godwin and Crews, 1999; reviewed in Crews and Sakata, 2000), and it is possible that *C. inornatus* males have fewer TH-IR cells in the pvPOA relative to *C. uniparens* individuals.

In this study, we used only *C. inornatus* males that were sensitive to the activational effects of P on courtship behavior (i.e., P-sensitive males). This is because P-sensitive males are hypothesized to have been involved in the hybridization events leading to *C. uniparens* (Crews, 1989; Crews and Sakata, 2000). We have preliminary evidence that P-sensitivity modulates the capacity of SKF to elicit mounting behavior, although the sample sizes are small. We found that the effective dose (0.05 μg/kg) used in P-sensitive males did not significantly decrease mount latencies in P-insensitive males ($n = 5$) relative to males treated with vehicle ($n = 5$). The effects of lower or higher doses, however, are not known, so we cannot definitively argue that P-sensitive males are more sensitive to SKF than P-insensitive males. Nevertheless, this suggests that P-sensitivity affects DA sensitivity. It is possible that, due to the hybridization events putatively involving P-sensitive males, *C. uniparens* are more sensitive to the D1 agonist because they possess three copies of the genes required to activate courtship behavior with P. Because DA–PR interactions, such as the ligand-independent activation of PR by DA, are known to occur in other species (reviewed in Mani, Blaustein, and O'Malley, 1997), it is possible there exists an interaction between these two systems in the modulation and evolution of male-typical courtship behavior. With the current investigations of the interactions between steroid hormones and neurotransmitters in rodents (e.g., Mani, Allen, Clark, Blaustein, and O'Malley, 1994; O'Malley, Schrader, Mani, Smith, Weigel, Coneely, and Clark, 1995) understanding the evolution of mechanisms for both DA and P sensitivity in whiptail lizards may provide insight into interactions between these systems in other species.

It was surprising that we failed to find a traditional dose response to the agonist in either species. Rather, in both species, only one of the doses was effective in increasing mounting behavior. However, work on other behaviors using a variety of dopaminergic drugs, including amphetamine (Taylor and Snyder, 1971) as well as more specific D1 agonists (such as SKF 82958 and SKF 77434; Shelf and Stein, 1992), have found similar all-or-none behavioral responses when using a broad range of doses (e.g., doses separated by a factor of 10), but found more gradual responses in a narrower range. We predict that, for example, doses between 0.005 and 0.05 μg/kg in *C. uniparens* and *C. inornatus* will also be somewhat effective in increasing mounting behavior.

Finally, although the SKF was capable of increasing mounting behaviors in both species, there were no increases in the expression of other copulatory behaviors. That there is such a sharp division between the ability of DA to increase mounting but not subsequent behaviors in the hierarchy raises questions about the involvement of other DA receptors or other neurochemical systems. For example, whereas D1 receptor stimulation is important in the expression of the early components of copulatory behavior, stimulation of D2 receptors is important in the expression of ejaculatory behavior in rodents (reviewed in Melis and Argiolas, 1995). Therefore, it is possible that D2 receptor stimulation could be required for neckgrip and intromission behaviors in whiptail lizards. An additional possibility is that DA alone is not sufficient to increase the expression of all aspects of male copulatory behaviors but rather priming by steroid hormones is necessary to fully facilitate the expression of the entire suite of sexual behaviors.

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