

Apomorphine effects on frog locomotor behavior

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Abstract

The neuroanatomical pathways of the DA systems have been shown to be largely conserved across many vertebrate taxa. It is less certain whether the structural similarities seen between mammals and amphibians reflect a similar functional homology. DA is well known for its role in facilitating motor behaviors in mammals. We examined whether a similar role for DA exists in amphibians using the Northern Leopard Frog (*Rana pipiens*). We investigated the effects of the nonspecific DA agonist, apomorphine (APO) on a complex motor task that included two distinct components known to be differentially modulated by DA in mammals: swimming and climbing. We demonstrated that a high single dose of APO (20 mg/kg, body weight) strongly increased the amount of time spent completing the motor task. Furthermore, we showed that although APO did not significantly alter several aspects of swimming behavior, two aspects of climbing behavior were disrupted. Both climbing speed and climbing ability were impaired by APO treatment. These results increase our understanding of DA function in amphibians and add to our understanding of structure–function homologies of dopamine function across vertebrate taxa.

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The neurotransmitter dopamine (DA) is known for its classic behavioral roles that include regulation of locomotion, mediation of reward and reinforcement behaviors and modulation of sex-specific behaviors. These behaviors have been shown to depend on DA circuits in the nigrostriatal pathway, mesolimbic pathway and medial preoptic area, respectively. Neuroanatomical studies of major vertebrate taxonomic groups provide strong evidence that DA pathways and cell populations are anatomically conserved across amniotes — mammals, birds and reptiles, and anamniotes — amphibians and fish [1]. Among studies of amphibians, developmental, hodological, and immunocytochemical studies have shown that anurans (frogs and toads) possess several DA cell populations homologous to those in mammals, including dopaminergic cell populations in the preoptic area, suprachiasmatic nucleus (believed to homologous to the mammalian arcuate nucleus cell population) and at the diencephalic-midbrain border adjacent to the

posterior tuberculum [2,3]. Marin et al. has shown that this midbrain DA population in anurans is connectionally most similar to the substantia nigra (A9) and ventral tegmental area (A10) of mammals and forms the DA input of the basal ganglia [2]. In addition to the DA pathways of the basal ganglia, much of the cytoarchitecture and neurochemistry of the striatum, as well as its afferent and efferent connections are also strongly conserved across major vertebrate taxa [4].

Although the neuroanatomy of central DA pathways has been well examined for nearly all major vertebrate taxa, far fewer studies have examined correlative DA function from a comparative perspective. The vast majority of studies examining the behavioral role of DA have focused on its significance in human and non-human primates, rodents and to a far lesser extent, in birds. These studies have implicated DA as an important modulator of behavior in three major functional domains, motor behavior, reinforcement and reproduction. Birds, like mammals, show increased locomotion and enhanced conditioned place preference to cocaine administration [5,6] and administration of various DA receptor

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specific ligands modulates both appetitive and consummatory aspects of Japanese Quail reproductive behavior [7,8]. Less is known about behavioral DA function in reptiles. However, DA ligands have been shown to modulate motor functions in snakes [9–11] and may modulate courtship behavior in whip-tail lizards [12].

Some studies have examined DA effects on a few motor behaviors in amphibians. Recently, Endopols et al. demonstrated that the use of the selective neurotoxin 6-hydroxydopamine (6-OHDA) to lesion DA neurons resulted in a dose dependent reduction of locomotor responses in a phonotaxis paradigm in female gray tree frogs, a motor behavior in which gravid females will move towards the call of a conspecific male [12]. In addition to reducing the number of subjects responding to the stimuli, all respondents showed an increase in latency to begin movement and a decrease in overall locomotor speed. Immunocytochemical analysis of tyrosine hydroxylase staining indicated a global degeneration of almost all DA fibers and several DA cell populations including those in the suprachiasmatic nucleus and posterior tubercular region. Although multiple DA populations were affected by 6-OHDA lesions, this work supports the role for DA in mediating locomotor behavior. Although female phonotaxis is a critical component of appetitive sexual behavior in these animals (a DA-mediated function in mammals), due to the global nature of motor deficit observed, it would be impossible to assess the role of DA in mediating appetitive behavior in this paradigm.

Glagow and Ewert have examined the effects of the DA mixed agonist, apomorphine (APO) on both appetitive and consummatory components of prey capture behavior in toads [13–15]. In the common toad, *Bufo bufo*, visual prey capture behavior consists of appetitive aspects such as orientation, approaching and turning, and consummatory aspects such as snapping. APO has been shown to impair orienting and turning, but facilitates snapping in a stereotyped manner. Anatomical studies using 14C-2 deoxyglucose (2-DG) mapping indicate that APO administration combined with a visual prey stimulus induced increases in 2-DG uptake in retinal projection regions, but induced decreases in 2-DG uptake in the striatum [13]. These authors suggest that prey capture consummatory behavior is facilitated by APO effects on retinal projection regions, while prey capture appetitive behavior is impaired due to APO effects on striatal function.

The remaining studies examining dopaminergic influences on amphibian motor behavior have shown that dopaminergic ligands do affect general motor responses such as righting reflexes or freezing behaviors [16–18]. These studies have indicated drugs that inhibit DA function such as haloperidol, a D2 antagonist, and the neurotoxin *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and impair motor responses in frogs as they do in mammals.

In this study we used *Rana pipiens*, the Northern Leopard Frog, to examine the effects of the APO on two behaviors that have been previously unexamined with regard to DA function in amphibians, swimming and climbing behaviors. Swimming and climbing are excellent behaviors for the examina-

tion of DA control of motor processes. Although both are complex behaviors, climbing and swimming are kinematically distinct. Climbing behavior requires vertical, ballistic, weight-shifting movement that opposes gravitational pull, whereas swimming behavior does not. Climbing behavior in rodents has been shown to be highly sensitive to DA manipulation. Mice show an increase in stereotyped climbing behaviors when administered with APO [19] and rats show dose dependent effects of APO on climbing to escape a forced swim test [19,20]. Lower doses of APO facilitate climbing, while higher doses impair climbing ability. In contrast, rats and humans with severe DA depletion can show effective swimming behaviors [21–23] and the Morris Water Maze is a commonly used task to assess cognitive deficits in 6-OHDA lesioned rats.

Previous studies in toads indicated that at a single high dose, APO alters both appetitive and consummatory aspects of prey capture behavior. Due to the paucity of behavioral studies examining APO effects on amphibian behavior, in these present studies we chose to examine the effects of a similar high dose in frogs in order to provide a context for interpreting our results. We examined the effects of a single high dose of APO on both swimming and climbing behaviors in *R. pipiens*. We predicted that if the amphibian dopaminergic system is functionally similar to that of mammals, APO would have differential effects on these two distinct behaviors. We hypothesized that APO would have no effect on swim behaviors, but would influence climbing behaviors in these animals.

1. Methods

1.1. Apparatus

All trials occurred in a stainless steel enclosure (56×56×26 cm). The arena was filled with fresh water everyday during the course of the experiment. In one corner of the arena a stack of two standard-sized bricks formed a rectangular platform. The platform extended 2.5 cm above water level. A clear Plexiglas top was placed on the top of the enclosure.

In pilot studies, when the water was maintained at preferred housing temperatures (22–24 °C) [24], subjects spent the majority of the time in each trial floating. Increasing the temperature to 28 °C, resulted in animals learning to swim towards and climb on the platform during Day 1 learning trials.

1.2. Animals

Sixteen male adult *R. pipiens* were purchased from Charles Sullivan, Inc (Nashville, TN). The experiment was performed in February 1997 after animals had been maintained in the laboratory for several months. Animals were housed in semi-aquatic conditions in groups of 8 in 40 l-sized aquaria and fed live crickets twice a week. A 12L:12D light cycle was maintained. All animal procedures were carried out in accordance to guidelines established by the University of Texas Institutional Animal Care and Use Committee.

1.3. Behavioral training

1.3.1. Practice trials

Each animal was placed in the corner opposite and facing away from the platform. Upon release, the animal was allowed to swim freely until it climbed onto the platform. The animal was allowed to remain on the platform for a 5-minute inter-trial interval. Each animal was given a total of four practice trials.

1.3.2. Learning trials

Following the fourth trial each animal was given an injection of 0.9% NaCl, i.p. (~250 μ l/animal) and placed into a dark box for 10 min. This injection served to expose the animals to the injection procedure. Animals were removed from the box and given as many trials as could be completed in 1 h following the injection using the same procedure as described above (trials ranged from 8 to 9/animal).

1.3.3. Testing trials

On the following day, each subject was given four trials prior to receiving the drug injection. Animals were then removed from the arena and given an injection of either apomorphine (20 mg/kg, bw) or an equivalent volume of 0.9% NaCl and placed into a dark box to minimize post-injection stress. Each animal was given as many trials as could be successfully completed in 1 h following the injection. If an animal was unable to climb onto the platform 5 min following the start of the trial, it was placed on the platform by the experimenter and given a 5-minute inter-trial interval prior to the next trial.

1.4. Behavioral measurements

Each trial was observed remotely on a video screen in an adjacent room. All trials were also videotaped for subsequent behavioral scoring. Behaviors scored included: swim patterns and distance, average time to complete a trial within the one hour session ("Trial Time"), average time to swim to *initially* reach the platform ("Swim Time"), the number of attempts made prior to successfully climbing onto the platform ("Climb Attempts"), and the average time spent of the final attempt to climb onto the platform ("Climb Time"). An attempt was defined as a continuous climbing motion. If the animal either swam away or paused before climbing the platform again, the behavior was scored as a separate climbing attempt. All drug conditions and behavioral scoring were performed blind as to treatment. Video recordings of two animals from the control condition were accidentally erased. These subjects were not used in the behavioral analyses.

1.5. Non-temporal swim behaviors

In addition to time measurements, we also examined other aspects of swimming behavior, such as pattern and distance, comparing Day 2 to Day 1 performances across drug treatments. Changes in motor pattern, such as increased thigmotaxis (the tendency to remain close to walls) are used in mammalian models as an indicator of increased stress and are known to be

sensitive to dopaminergic influence [25]. Measuring swim distance examines whether APO specifically altered swimming speed or some more qualitative aspect of motor behavior.

1.6. Drugs

Apomorphine (Sigma, St. Louis, MO) was prepared in 5 mM of ascorbic acid (2 mg/ml). Drugs were kept in foil to prevent light exposure, and stored at -20°C until use. 0.9% NaCl was stored in a similar manner. All vials were coded such that experimental trials were performed blind to treatment.

1.7. Statistical analyses

Statistical analyses were performed comparing APO- and saline-treated animals. Several variables were examined: Trial Time, Swim Time, Climb Time and Climb Attempts. Due to vast differences in individual performances for Swim Time, statistical comparisons of both Trial Time and Swim Time were based on a relative change from Day 1 (i.e. average Day 2 time minus average Day 1 time). A positive score reflected an increased in Swim Time on Day 2 relative to Day 1, while a negative score reflected a decreased Swim Time. In contrast, there was little individual difference in Climb Time among animals, therefore comparisons could be made by examining absolute time across treatment on Day 2. Two-tailed *T*-tests were used to assess all differences between APO- and saline-treated animals. Only post-injection trials were used for behavioral comparisons. All values are reported as mean \pm SEM.

2. Results

2.1. Overall behaviors

There were no observable differences in swim patterns or distance traveled comparing APO and saline animals (data not shown), therefore these variables were not further examined.

Behaviors in the arena were divided into two categories: swimming and climbing. Swimming behavior consisted of a combination of synchronous kicking of the hind limbs, asynchronous kicking of the hind limbs and gliding. Climbing behavior consisted of alternating bilateral movements of both fore- and hind limbs which commenced when an animal's forelimb came in contact with the side of the platform (or side of the tank). Occasionally, animals were observed to hop directly from the water to the platform.

2.2. Effects of APO on swimming and climbing behavior

An initial comparison examining changes in Trial Time for APO- and saline-treated animals indicated that compared to Day 1 trial times, the average time to complete the trials was significantly increased in APO-treated animals ($t(12)=2.6$, $p=0.02$) (Fig. 1). The average relative Trial Time was 49.52 ± 19.03 s for APO animals compared to -4.68 ± 11.23 s for controls. A closer examination of two behavioral components within Trial Time indicated that there was no statistical

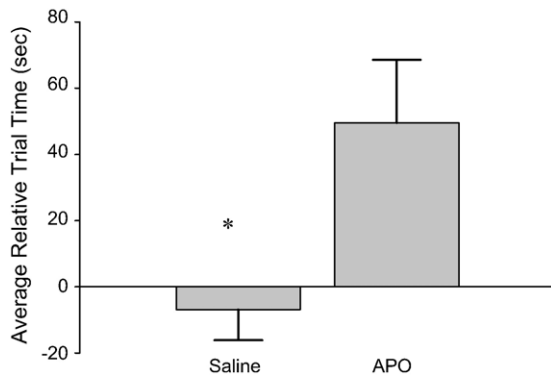


Fig. 1. Mean \pm SEM of the average Trial Time relative to Day 1 for saline and APO-treated animals. APO-treated animals averaged significantly more time per trial compared to control animals (* $p < 0.05$).

difference in relative Swim Time to initially reach the platform between the APO- and saline-treated animals ($t(13) = 0.23$, n.s.) (Fig. 2A). However, APO-treated animals differed significantly from control animals in two measures of climbing behavior. First, APO treatment altered the number of attempts required to climb out of the arena. On Day 1, virtually all animals were able to climb out of the area onto the platform on the first attempt. Examination of Day 2 performance indicated that APO animals required significantly more attempts at climbing to successfully reach the dry platform ($t(8) = 3.37$, $p = 0.01$) (Fig. 3). Furthermore, the time spent climbing during the final successful

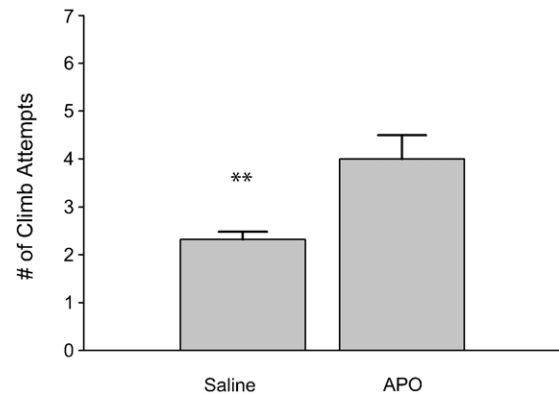


Fig. 3. Mean \pm SEM of the average number of attempts before animals were able to successfully climb onto the platform on Day 2. APO-treated animals required significantly more attempts to climb onto the platform compared to control animals (** $p < 0.025$).

attempt was increased in APO-treated animals ($t(12) = 2.787$, $p = 0.016$) suggesting that climbing behavior was impaired as well (Fig. 2B).

3. Discussion

This study demonstrates that a single high dose of APO impairs domain specific motor behaviors in frogs. Following an injection of 20 mg/kg APO, i.p., male *R. pipiens* were tested for changes in motor ability in a learned swim-climb paradigm. Following injection, frogs continued to be able to complete the task. However, animals showed a specific impairment in ability to climb from the arena onto the dry platform, but not in swimming ability or speed. This differential effect of APO on swimming and climbing is comparable to that seen following manipulation of the nigrostriatal DA system in rodents. These present results add to our knowledge of DA-mediated behaviors in amphibians and are consistent with other studies in amphibians and other vertebrates that indicate that APO influences DA-mediated locomotor behaviors.

In this study, a learned swim-climb paradigm was used to assess DA-mediated motor behaviors in frogs. Frogs were easily trained to associate swimming towards a dry platform with an opportunity to climb out of the water. Following acquisition of the task, all animals were able to locate and navigate towards the platform without difficulty. A single high dose of APO did not influence the animals' ability to locate the platform, nor did it influence speed or direction of swimming behavior in frogs. However, climbing behaviors were greatly impaired. In comparison, studies in rats have shown that both systemic and striatal injections of APO can influence swimming, floating and climbing behavior in rats in a dose dependent fashion. In low doses, APO enhances these behaviors, while higher doses impair these motor tasks [20,26].

Although studies in rats have shown that swimming can be influenced by APO treatment in forced swim tests, several studies have brought to question whether swimming behavior is actually a DA-dependent function. Studies examining the effects of bilateral depletion of DA following 6-OHDA lesions have shown

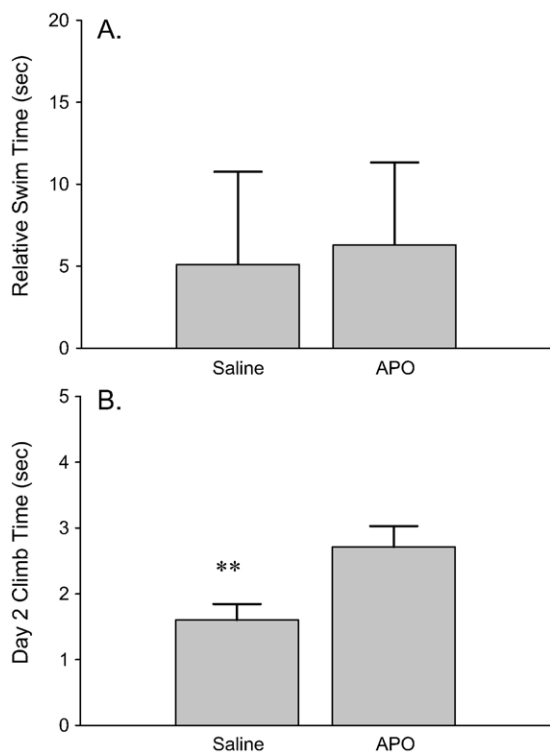


Fig. 2. Mean \pm SEM of two different time components of Trial Time for saline and APO-treated animals. A. Swim Time — there was no difference between treatments for relative time spent swimming to the platform. B. Climb Time — on Day 2, APO-treated animals spent significantly more time climbing onto the platform compared to control animals (** $p < 0.025$).

that although rats exhibited multiple deficits in cognition involving swimming-based maze tasks, swimming ability *per se* was not affected [21,27]. Furthermore, Keefe et al. [22] demonstrated that DA depleted rats that exhibited akinesia on land could still swim effectively when placed in water.

In contrast, climbing is a qualitatively distinct motor behavior compared to swimming. Climbing behavior requires rapid, gravity-opposing, vertical weight shift, compared to the horizontal movements of swimming. Results from this study are consistent with findings in mammals that high doses of APO impair animals' ability to climb out of water. In this study, APO-treated frogs showed an increase in the number of attempts required in order to climb onto the platform and more time to execute the climb. Although APO can cause stereotyped climbing behaviors in mice [19], several studies have shown that rats with nigrostriatal impairment have difficulty with initiation of weight-shifting behaviors such as climbing, but not swimming behaviors [21,27,28].

APO administration can facilitate DA-mediated behaviors such as locomotion, swimming and copulation in animals with reduced dopaminergic function (aged animals or animals with DA lesions). However at higher doses APO has been shown to impair those same behaviors as stereotyped movements are induced. The dose dependent effects of APO are well known as the drug acts non-selectively on both post-synaptic (D1 and D2) and pre-synaptic autoreceptors (mainly D2). Agonists binding to autoreceptors would result in feedback inhibition of DA function. Although the systemic administration of APO in this study made it impossible to identify its location of action, we had hypothesized that APO would preferentially impair locomotion based upon two lines of evidence. First, prior studies demonstrated that APO administered at 20 mg/kg body weight in toads impaired such weight-shifting behaviors as turning and lunging [13,15]. Second, pharmacological studies of D2 receptor agonists, such as APO, in general impair locomotor abilities [29]. The results of this study support our conclusion that APO at this dose impairs climbing behavior via its effect on disrupting DA function.

Although this present study examined the role of DA within the context of controlling motor behaviors, the interpretation of the data from this study would be incomplete if other behavioral effects of DA were not considered. DA is well known for its role in mediating reward and reinforcement, behavioral aspects which reflect motivation. In this study, average Trial Time following APO administration was significantly increased due to impairments in climbing ability. However, it is possible that motivation to climb from the water was affected as well. Two aspects of motivation in this paradigm bear closer examination. The first is the lack of distinction between ability to climb and motivation to climb onto the platform. In this study, there was no difference between groups in the ability to swim to the platform (Swim Time), however many animals did not climb out upon reaching the platform (Trial Time). Impaired climbing ability did contribute to the increased Trial Time of APO-treated animals. However, in this paradigm it was impossible to examine whether a reduction in motivation may have influenced this

variable as well. One other aspect not considered in this study was the reward salience of the inter-trial interval. One pervading theory regarding DA's role in controlling reward and reinforcement is that DA mediates the salience of reward stimuli [30]. High doses of APO in rodents have been shown to reduce reward seeking behavior [31,32]. In this study, the 5-minute inter-trial interval served as a "reward" for successfully climbing onto the platform. Whether this "reward" value changed as a function of APO administration and therefore influenced behavior in this study is unknown.

Although the role of DA in mediating reward and reinforcement has been well examined in mammalian models and now has been examined in birds [5,6], little is known regarding the role of DA-mediating reward or reinforcement in a non-endotherm. Recently it has been shown that D-amphetamine induces conditioned place preference in the green tree frog, *Hyla cinerea* [33]. These studies combined provide evidence that DA may mediate both motor and reward aspects of amphibian behavior. The results of this present study are not only consistent with previous studies that provide evidence for DA-mediating motor behaviors in frogs [13,16–18,34], these studies combined indicate an evolutionary conservation of DA function across vertebrate taxa.

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