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The effect of dopamine receptor blockade on motor behavior in *Aplysia californica*

Jane M. Flinn[a,*], Peter Gochman[a], Patricia Wanschura[a], Vikas Chandhoke[b]

[a]*Department of Psychology, MSN3F5, George Mason University, Fairfax, VA 22030-4444, USA*
[b]*Department of Biology, George Mason University, Fairfax, VA 22030-4444, USA*

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Abstract

The mammalian D1- and D2-like receptor blockers SCH-23390 and raclopride were used to block receptors in *Aplysia californica*, and the effect on reflexes and escape behavior was examined. Four groups of 20 young adults were each injected with SCH-23390, raclopride, SCH-23390 + raclopride, or seawater. The drug (0.0125 mg/g of body weight) was injected 2 mm anterior to the parapodia. After the injection of either SCH-23390 or SCH-23390 + raclopride, there was a significant increase in parapodia opening ($P < .001$), siphon withdrawal ($P < .05$), and galloping following tail pinch ($P < .01$) compared to raclopride-injected or control animals. The data showed that blockade of receptors by SCH-23390, but not raclopride, produced significant changes in motor behavior in *A. californica*.

Keywords: SCH-23390; Raclopride; Receptor; Dopamine; *Aplysia californica*; Locomotion; Motor reflexes

1. Introduction

The neurotransmitter dopamine (DA) is found in animals ranging from invertebrates to primates. DA receptors are of two major types, the D1- and D2-like, each having a subset of receptors D1/D5 and D2/D3/D4, respectively. D1-like receptors increase adenylate cyclase activity, whereas the D2-like receptors either decrease or do not affect it (for reviews, see Niznik, 1994; Robinson and Caron, 1997). Both D1- and D2-like receptors can be pre- or postsynaptic (Grenhoff and Johnson, 1997). DA plays an important role in movement in invertebrates and mammals, while imbalances in the DA system have been associated with Parkinson's disease and schizophrenia in humans. Both the D1- and D2-like receptors are involved in motor behavior, whereas neuroleptic drugs primarily block the D2-like receptors, with varying degrees of specificity.

DA is a common neurotransmitter in molluscs. Because of their relatively simple nervous systems and the possibility of identifying individual neurons, the role of DA and the effects of various DA agonists and antagonists have been examined in several molluscan species (for review, see Sugamori et al., 1994). DA is found both in the cell bodies and in the neuropile of the CNS in *Aplysia californica* (Goldstein and Schwartz, 1989; McCaman et al., 1973). The highest levels are in the neuropile of the pedal ganglia (McCaman et al., 1973), which are involved in motor control (Hening et al., 1979; Jahan-Parwar and Fredman, 1979). High levels of DA are also found in peripheral nerves (Goldstein and Schwartz, 1989; McCaman et al., 1973; Swann et al., 1982a,b,c) and in the gill (Peretz and Estes, 1974).

DA receptors are generally found on axons rather than cell bodies, the highest levels being found in the pleural ganglia, which modulate locomotion (Ascher, 1972; Drummond et al., 1978, 1980; Jahan-Parwar and Fredman, 1979). DA receptors are also found on gill muscle, where DA acts both as a neurotransmitter and as a neuromodulator (Drummond et al., 1980; Ruben and Lukowiak, 1983; Ruben et al., 1979; Swann et al., 1982a,b,c). DA enhances gill contractions following siphon touch, and prevents habituation of the gill and siphon withdrawal reflex (Ruben and Lukowiak, 1979, 1983).

The DA receptors in *A. californica* are not well characterized, although Lo and Weiss (1994) have cloned two G-protein-coupled *Aplysia* receptors, which have high homology to mammalian D1-like receptors, and Southall et al.

* Corresponding author. Tel.: +1-703-993-4107; fax: +1-703-993-1359.
E-mail address: jflinn@gmu.edu (J.M. Flinn).

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(1995) have used specific mammalian antagonists to examine the changes in the D1, D2, D3, and D4 receptors across the life span. DA activates both cAMP and adenylate cyclase in the gill (Kebabian et al., 1979; Weiss and Drummond, 1981), presumably through D1-like receptors. Excitatory and inhibitory responses to DA are mediated by two different types of receptors in *A. californica* (Ascher, 1972). Inhibition in the pleural ganglia is due to increased potassium conductance (Ascher, 1972). Yaari (1988) has shown potassium channels are activated by D2-like receptors, which do not inhibit adenylate cyclase, but may activate the arachidonic acid pathway. Comparisons of neuroleptic and antidepressant drugs showed that the neuroleptic drugs fluphenazine, clozapine, chlorpromazine, and haloperidol blocked all DA responses, which antidepressants did not (Davies, 1981; Heiss and Hoyer, 1974). The results "correlated well with reported antidopaminergic activities of these drugs in animals and patients" (Davies, 1981). All invertebrate DA receptors do not correspond to mammalian types (Sugamori et al., 1994), but there appears to be a reasonable homology in *A. californica*. However, the bursting neuron R15 has unusual dopaminergic properties (Gospe and Wilson, 1981).

Considering the role of DA in locomotion in other species, its presence in the pedal ganglia and its effect on gill muscle, we have begun to examine its role in locomotion in *Aplysia*. Locomotion in *A. californica* is in the form of pedal waves with both longitudinal and transverse contractions (Hening et al., 1979), and can take two forms, gliding and galloping. There is little transverse contraction in the gliding condition, and the foot remains close to the substrate. In the type of locomotion called "galloping" by Jahan-Parwar and Fredman (1979), an exaggerated head extension occurs, the medial part of the foot leaves the substrate forming an arch, and this is followed by tail release. After an aversive stimulus to the tail, an animal will typically show a generalized contraction, initiate movement by galloping, and then switch to gliding.

DA receptor blockers with improved selectivity are now available. We have examined the effect of SCH-23390 and raclopride, which are specific to the D1- and D2-like families, respectively, in mammals, and are water-soluble. We report here the effect of receptor blockade using these drugs on siphon, posterior tentacle (rhinophore) and foot withdrawal, parapodia opening, and escape behavior in *A. californica*.

2. Method

Eighty adult *A. californica* from the Aplysia Facility at the University of Miami, 5–6 months of age (posthatch), were used in the study, and housed in tanks containing artificial seawater (ASW) at 18°C, with a 12-h light–dark cycle. Animals were maintained for 5 days prior to experimentation and then randomly assigned to one of four groups in which (i) receptors were blocked by SCH-23390, (ii) receptors were blocked by raclopride, and (iii) receptors were blocked by a combination of the drugs, or (iv) seawater was injected. The animals were weighed prior to drug injection. The level of drug injected was 0.0125 mg × body weight in grams, with larger animals receiving larger doses. This level was chosen following preliminary experiments, which determined that these levels of SCH-23390 or raclopride did not cause any change in ongoing behavior. A larger dose of 0.025 mg/g of raclopride led to reduced normal movement. Specific sensory–motor responses were enhanced following the administration of this level of SCH-23390. The average weight of the animals was 53 g. The drugs were injected 2 mm anterior to the parapodia along the dorsal midline, at a 45° angle towards the head; the syringe needles were 1 cm long. The parapodia ratio, defined as the maximum separation of the parapodia, divided by the length of the parapodia (see Fig. 1a), was measured before, as well as after, drug administration by an observer blind to the drug condition.

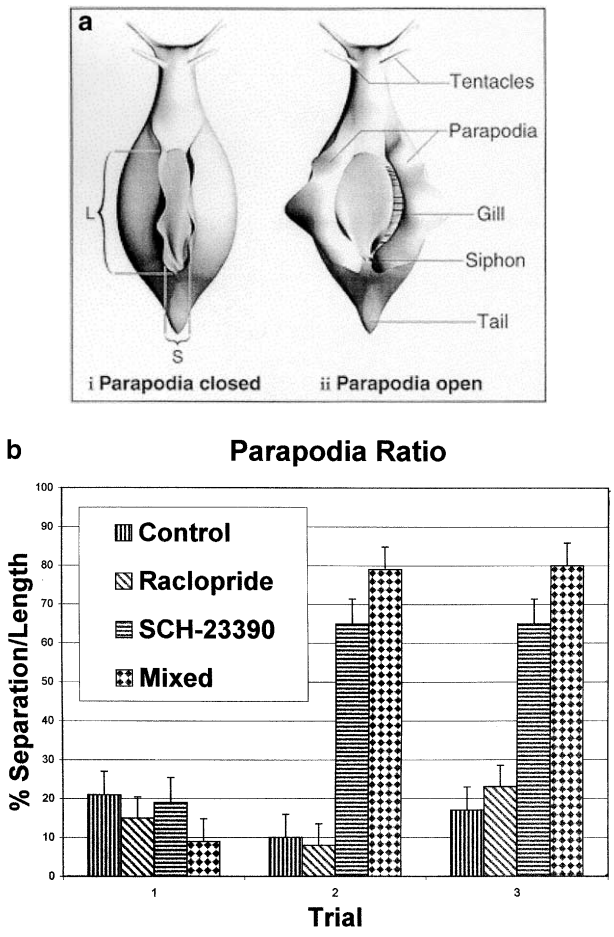

Fig. 1. (a) The parapodia ratio was defined as the maximum separation of the parapodia (*S*) divided by the length of the parapodia (*L*). The parapodia are normally closed as shown on the left. Injection of SCH-23390 or SCH-23390 + raclopride caused the parapodia to open significantly. (b) The effect of raclopride and SCH-23390 on parapodia opening. Each bar represents the mean and S.E.M. of 20 observations. Trial 1 was immediately before drug administration, Trial 2 was 5 min later, and Trial 3 was 30 min later.

Five minutes after drug injection, the animals were placed in a 5 × 5-ft Plexiglas ASW-filled container, with a 1-in. grid on the floor for behavioral measurements. The parapodia ratio was then measured again. Following this, light touches, using a metal spatula and lasting less than 1 s, were made to the left posterior tentacle, the siphon, and the foot, in this order. The responses were classified on a 1–3 scale as: (1) no response; (2) withdrawal; (3) strong response. Response type 3 included balling of the body to tentacle or siphon touch, and locomotion to tail touch. Responses were scored by an observer blind to the condition of the animal.

Following the three light touches, the animal was placed in the center of the tank and the tail pinched twice, using inverted hemostatic forceps. The jaws closed with a force of 9.8 N. Two pinches each lasting 1 s, were given 1 s apart, and the animals' locomotor behavior was observed and measured for 5 min. This procedure was repeated three times. The behaviors observed included the: (i) number of arches (arching), (ii) distance traveled during galloping (galloping), and (iii) total distance moved (distance). An "arch" is defined as the medial portion of the animals' foot leaving the substrate (see Fig. 2), followed by a release of the posterior part of the foot from the substrate. There were two observers, one of whom was blind to the group to which the animal belonged. Interrater reliability was .92. Galloping was defined as locomotion that took place while the animal was arching; the distance traveled during galloping was measured in body lengths. Animals also moved by "gliding" in which case the medial part of the foot did not leave the surface. The total distance moved by the animals, using both escape locomotion and gliding, was measured in body lengths. The parapodia ratio was measured for the third time at the end of the locomotion experiments.

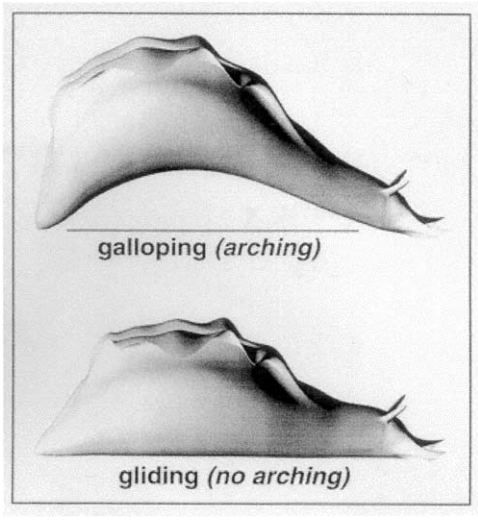

Fig. 2. Two modes of locomotion, galloping and gliding, were seen following tail pinch. Galloping, in which the animal forms an arch with the medial part of the foot leaving the surface is shown on the left. The number of arches formed and the distance moved while galloping were significantly greater after injection of SCH-23390 or SCH-23390 + raclopride. SCH-23390 blocks D1-like receptors, while raclopride blocks D2-like receptors.

3. Results

The greatest effect of receptor blocking was seen in the opening of the parapodia, measured by the parapodia ratio, as shown in Fig. 1. The animals in the SCH-23390 or combined-drugs groups showed a significant increase in the parapodia ratio after drug injection, whereas those in the raclopride and control groups did not. After drug administration, the SCH-23390 group had a parapodia ratio value about three times that of the controls; for the combined-drugs group the parapodia ratio value after drug administration was about four times that of the controls, whereas there was no significant difference beforehand. A repeated measures ANOVA (RMANOVA) showed that there were significant differences between drug groups, $F(3,76) = 21.64$, $P < .001$. There was a significant change over successive trials, $F(2,76) = 22.78$, $P < .001$, and a Trials × Drug interaction, $F(6,76) = 12.66$, $P < .001$. A simple effects analysis showed that there was no significant difference between any of the groups before administration of the drugs. However, the parapodia ratio for both the SCH-23390 and the combined-drugs groups increased significantly between trials given before and after drug administration, $F(2,19) = 14.86$ and 35.50, respectively, $P < .001$. The changes were seen both immediately after drug delivery (Trial 2) and 30 min later (Trial 3). Tukey's post hoc tests showed that the parapodia ratios of the SCH-23390 and combined-drugs groups were significantly greater than all other values, $P < .05$, but they did not differ significantly from each other for either Trial 2 or Trial 3.

The animals' movement following tail pinch was measured three times for each of the variables arching, galloping, and distance. Data from all three trials were analyzed for each of the variables using RMANOVAs. Since no effect of trials was observed, and there was no interaction between drugs and trials, the results of the three trials were summed together for each variable and this was used in one-way ANOVAs; the results of which are presented here. The means and standard deviations for the summed data are given in Table 1, There was a significant difference between the four groups for arching, $F(3,76) = 18.95$, $P < .001$, and for galloping, $F(3,76) = 12.48$, $P < .001$. Tukey's post hoc tests showed that both the SCH-23390 and the combined-drugs groups had significantly more arches and moved significantly further while galloping than either the raclopride or control groups ($P < .01$). No other significant differences between groups were seen. There were no significant differences in total body lengths traveled (distance) for any of the groups, $F(3,76) = 1.69$, NS.

The withdrawal responses to tentacle, siphon, and foot touch were each analyzed using χ^2. The frequency in the "no

Table 1
Means and standard deviations for behavior by drug group

	Control	Raclopride	SCH-23390	Combined-drugs
Locomotion following tail pinch				
Arching[a]	20.8 (13.0)	22.2 (13.3)	47.0 (22.6)	55.0 (22.6)
Galloping[a,b]	8.9 (5.7)	8.5 (5.6)	15.1 (7.0)	18.5 (5.7)
Distance[a,b]	15.6 (5.5)	17.1 (5.5)	16.4 (7.0)	19.7 (6.0)
Responses to light touch				
Siphon withdrawal	1.9 (0.79)	2.0 (0.75)	2.4 (0.46)	2.5 (0.47)
Anterior tentacle withdrawal	2.3 (0.52)	2.3 (0.52)	2.5 (0.51)	2.6 (0.63)
Foot withdrawal	1.9 (0.68)	1.9 (0.64)	2.0 (0.60)	2.3 (0.64)
Parapodia opening				
Parapodia ratio (Trial 1), %	21 (27)	15 (22)	19 (28)	9 (26)
Parapodia ratio (Trial 3), %	17 (29)	23 (36)	65 (38)	80 (33)

[a] For behavior summed over all three trials.
[b] In body lengths.

response'' category was expected to be small, and in fact only 5/80, or 6.25%, of animals failed to respond to tentacle touch. Therefore, the ''no response'' (Category 1) and ''some response'' (Category 2) results were combined in the analysis. The χ^2 analysis showed that there was a significant difference between the groups in siphon withdrawal, $\chi^2(3, N=80)=14.62$ ($P<.01$). Post hoc tests showed that the SCH-23390 and combined-drugs groups showed significantly greater siphon withdrawal than the raclopride and control groups, $\chi^2(1, N=80)=14.04$ $P<.01$. There were no significant differences between the SCH-23390 and combined-drugs groups, or between the raclopride and control groups, for siphon withdrawal. There were no significant differences between any of the groups in their responses for tentacle withdrawal, $\chi^2(3, N=80)=6.63$ (NS) or foot withdrawal, $\chi^2(3, N=80)=3.74$ (NS).

4. Discussion

This experiment showed that blocking receptors with SCH-23390 had a significant effect on some types of motor behavior in *A. californica*, whereas blocking the receptors with raclopride had no significant effect. The changes were greatest when both drugs were used, but were not significantly different from those seen when only SCH-23390 was used to block receptors. The greatest behavioral effect was seen in the spontaneous opening of the parapodia after drug administration in the SCH-23390 and combined-drugs groups, while the animals were at rest (see Fig. 1b).

The parapodia normally open and close rhythmically during locomotion, with greatest closing when the animal is most arched. They showed rhythmic movements during locomotion in this experiment, but the animals in which SCH-23390 or SCH-23390 + raclopride were used to block receptors had the most open parapodia. The rhythmic contractions are controlled by the cerebral, pleural, and pedal ganglia and are due to a central pattern generator (Hening et al., 1979; Jahan-Parwar and Fredman, 1978a,b). The parapodia can also close in response to peripheral stimuli, such as touch to the tentacles or siphon, a type of response that requires the abdominal ganglion (ibid.).

Application of DA to the gill increases cAMP (Weiss and Drummond, 1981) and causes gill contraction (Ruben and Lukowiak, 1979; Swann et al., 1982c), presumably via D1-like receptors. (In the present experiment, the gill was covered by the parapodia in the control and raclopride groups, and could not be well observed.) The gill contraction is due DA acting both as the transmitter at the neuromuscular junction and as a neuromodulator (Swann et al., 1982a,b,c). Whether the opening of the parapodia following use of SCH-23390 is due to a blockade of receptors on the parapodia muscles, and/or to effects in the central pattern generator, is not clear. However, ''uniquely high'' levels of DA have been found in the parapodial nerves, with regions near the parapodia having higher amounts than those near the ganglion (McCaman et al., 1973).

The withdrawal of the siphon following light touch showed a similar pattern of responses as parapodia opening. Blocking receptors with SCH-23390 significantly increased the withdrawal response, whereas blocking with raclopride did not. Blocking with both drugs led to the greatest response. These results suggest that DA plays a role in siphon as well as gill withdrawal.

Animals normally respond to an aversive stimulus to the tail by using galloping locomotion, with its associated arching, and then begin to glide. This behavior was seen in the control animals in this study and in the raclopride animals. However, animals in which SCH-23390 was used to block receptors used galloping behavior almost all the time. Some gliding was seen towards the end of the 5-min period their movement was observed, before they came to rest. The change in behavior was not due to a change in sensory threshold, because there was no change in tail withdrawal following light touch to the tail. Using raclopride as a blocking agent alone had no effect, although using

both drugs produced a nonsignificant enhancement as compared to using only SCH-23390. DA thus appears to inhibit transverse contractions and arching, possibly acting through D1-like receptors.

Locomotion waves are controlled by a central pattern generator in the pedal ganglia (Hening et al., 1979; Jahan-Parwar and Fredman, 1979). The waves are initiated by command neurons in the cerebral ganglia (Fredman and Jahan-Parwar, 1983), but the presence of galloping requires modulation from the pleural ganglia (Jahan-Parwar and Fredman, 1979), which have high levels of DA receptors (Drummond et al., 1980). Serotonergic pedal neurons fire in rhythmic bursts following aversive stimulation (McPherson and Blankenship, 1992) and locomotion can be triggered by serotonin (5-HT), which is released following tail shock, but not by DA (Mackey and Carew, 1983). In *Aplysia kurodai*, 5-HT can block the hyperpolarizing effect of DA (Shozushima, 1984). The galloping behavior normally seen after an aversive stimulus could be due to the release of 5-HT, initiating locomotion and overriding dopaminergic inhibition. The relative activity of serotonergic and dopaminergic neurons may thus control the presence or absence of arching.

The behavioral results show that SCH-23390, which blocks the D1-like receptors in mammals, significantly enhanced parapodia opening, siphon withdrawal, and galloping. In contrast, the neuroleptic drug raclopride, which blocks D2-like receptors in mammals, had no significant effect on these behavior when presented alone. Although, when the two drugs were presented together, raclopride consistently enhanced the effect of SCH-23390, but not at a statistically significant level.

Previous tests of neuroleptic drugs, such as fluphenazine, found them to affect both excitatory and inhibitory responses in *A. californica* (Davies, 1981; Heiss and Hoyer, 1974), but these drugs are less selective blockers than raclopride. In preliminary experiments, we found that fluphenazine led to bloated, unresponsive, "sick" animals, and it was not used for this reason. The difference in responses to fluphenazine, raclopride, and SCH-23390 shows that motor responses in *A. californica* can be used to give information about DA receptor blockers. This may be a useful behavioral assay with which to study the specificity of such drugs.

5. Conclusion

The behavioral results, summarized in Table 1 and Fig. 1, showed that the drugs SCH-23390 and raclopride, which block the D1- and D2-like receptors, respectively, in mammals had significantly different effects on motor behavior when used in *A. californica*. SCH-23390, significantly enhanced parapodia opening, siphon withdrawal, and galloping locomotion. Raclopride had no significant effect on these behaviors. Using both drugs together consistently produced greater effects than presenting SCH-23390 alone, but the difference was not statistically significant for any behavior. Receptors blocked by SCH-23390, possibly D1-like receptors, may play an important role in certain types of motor behavior in *A. californica*.

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