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Neuroleptic Modulation of Oral Dyskinesias Induced in Snakes by *Xenopus* Skin Mucus

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BARTHALMUS, G T *Neuroleptic modulation of oral dyskinesias induced in snakes by* Xenopus *skin mucus* PHARMACOL BIOCHEM BEHAV **34**(1) 95–99, 1989 —The skin mucus of the African clawed frog *Xenopus laevis* promotes escape from the American water snake *Nerodia sipedon* by inducing oral dyskinesias As *Xenopus* mucus contains peptides and indoleamines with known neuroleptic properties, and because neuroleptics are the chief cause of drug-induced orofacial dyskinesias in humans, the hypothesis was tested that the neuroleptic haloperidol (HAL) would induce oral dyskinesias when given alone and would potentiate dyskinesias in *Nerodia* if injected prior to oral application of *Xenopus* mucus Mucus alone induced yawning, gaping, fixed yawning, fixed gaping, writhing tongue movements, gular and chewing movements, and climbing behavior, but attenuated locomotor activity HAL given IP alone at 0 05 and 0 5 μg/g was ineffective However, HAL greatly potentiated mucus-induced yawning but attenuated the fixed gaping seen when only mucus was applied Data support the hypothesis that *Xenopus* skin mucus has neuroleptic properties and that *Xenopus'* antipredatory defense is in part related to chemical induction of orofacial and climbing behavior in snake predators

Xenopus skin mucus Yawning *Nerodia* Dyskinesia Neuroleptics Haloperidol CCK-8 Caerulein Xenopsin TRH Dopamine Climbing

THE poison (granular) gland contents of the skin of the African clawed frog, *Xenopus laevis*, induces orofacial dyskinesias that promote escape from the American water snake, *Nerodia sipedon*, without inducing flavor aversion (2) Mucus extracted from *Xenopus* skin and applied orally to *Nerodia* induces identical orofacial behaviors. Because the skin mucus contains peptides and indoleamines with neuroleptic (dopamine receptor-blocking) properties [see (2)], it was suggested that the mode of action of *Xenopus* skin mucus may be similar to that which underlies the orofacial movement disorders seen in animals and humans given dopamine receptor blockers This study tests the hypotheses that the neuroleptic haloperidol (HAL), a D2 dopamine receptor blocker, can induce oral dyskinesias alone in *Nerodia* and can potentiate the behaviors induced by *Xenopus* skin mucus

METHOD

The subjects (N = 6) were 14-month-old sibling *N sipedon* born in the laboratory during July 1987 Body weights at the beginning of the study (11–12 g) increased (16–23 g) during the 72-day investigation Individuals were reared in glass aquaria fitted with newspaper bedding and a water bowl, fed live minnows to repletion once each week, and were maintained on a photoperiod of 14 L 10 D at ambient laboratory temperatures Male *Xenopus* frogs (Xenopus I, Ann Arbor, MI), having a 4–5 cm body length, were reared in a flow-through tank at 18°C and a 12 L 12 D photoperiod, and were fed pelleted *Xenopus* chow (Carolina Biological Supply, Burlington, NC)

Procedure

Trials occurred in 40-l aquaria containing 3 cm of tap water at 26°C Each of two observers was assigned 3 snakes, Observer No 1 tested snakes A, C and E, and Observer No 2 examined snakes B, D and F. Two snakes, e g , A with B, C with D, and E with F were tested as a pair but within separate enclosures, a single frog served as a mucus donor for testing one pair of snakes. Thus, individual differences between two different snakes exposed to the mucus taken from the same frog could be assessed

Snakes were first administered haloperidol (Sigma Chemical) or drug vehicle (minimal 0 02 M acetic acid to dissolve the drug plus distilled water) and observed for 20 minutes Then, either frog mucus or porcine mucin (Sigma Chemical), a control for the physical presence of mucus in the mouth, was applied to the roof of a snake's mouth and behavior was recorded for an additional 40 minutes HAL at 0.05 or 0.5 μg/g body weight, or the drug vehicle was delivered IP ventro-laterally in 0.05 cc per 5 g body weight The white granular gland mucus was collected by injecting 0.012 mg epinephrine, dissolved in 0 2 cc tap water, into the dorsal lymph sac of *Xenopus* To prevent rapid drying and thickening of the mucus, tap water was first applied to a frog's back and to the spatula used for removing the mucus. Mucus was applied immediately to the dorsal surface of a snake's mouth The porcine mucin (sham control) was mixed with tap water to the

TABLE 1

MEAN OROFACIAL BEHAVIORS PER 40-MINUTE SESSION WHERE *XENOPUS* SKIN MUCUS WAS GIVEN ORALLY, TO 6 SNAKES, ALONE OR TOGETHER WITH 0 05 OR 0 5 μg/g BODY WEIGHT HALOPERIDOL (IP)

Behavior	Mucus and Vehicle	Mucus and 0 05 HAL	Mucus and 0 5 HAL	1 S E *	F†	$p>F$
Gaping	38 2	38 2	49 6	4 1	2 5	0 1296
Fix Gaping‡	48 7 (a)¶	4 0 (b)	3 6 (b)	4 3	61 1	0 0001§
Yawning‡	3 5 (a)	50 7 (b)	58 8 (b)	5 5	54 7	0 0001§
Fix Yawning	0 3	0 7	0 8	0 3	0 7	0 4960
Gular‡	3 4	6 4	3 0	1 3	1 2	0 3308
Chewing‡	3 0 (a)	6 4 (b)	9 7 (b)	1 6	8 3	0 0074§
Writhing Tongue	23 6	17 7	17 6	2 9	1 4	0 2978
Mean Totals	120 7	124 1	143 1			

*Standard error of a mean calculated using the Snake × Drug mean square from the ANOVA
†ANOVA F-test for no difference between the three drug doses
‡Square root-transformed data
§Highly significant mucus-haloperidol interaction
¶Within a row, means without a common letter in parentheses differ significantly using the protected LSD at the 5 percent level

consistency of the fresh frog mucus As *Xenopus* were reared in tap water and snakes were tested in the same, and because water may leak from the site where epinephrine was injected under the frog's skin, tap water rather than saline or deionized water was used Saline softens fresh mucus, altering the consistency in which it is found in natural waters Further, because orally applied mucin and mucus make immediate contact with the tap water in the test aquarium, tap water was used in their preparation

Three replicate trials for each of 6 treatments were performed on 6 snakes Replicate determinations were performed every 4 days The treatments and the order of treatments were as follows vehicle and sham mucin, vehicle and frog mucus, 0 05 μg/g HAL and sham mucin, 0 05 μg/g HAL and frog mucus, 0 5 μg/g HAL and sham mucin, 0 5 μg/g HAL and frog mucus

Behaviors Recorded

Orofacial behaviors observed included *Gaping* (G)—slight opening then closing of the mouth, *Yawning* (Y)—wide prolonged opening then closing of the mouth, often with the head dorsoflexed, *Fixed Gaping* (FG)—gaping longer than 4 seconds, *Fixed Yawning* (FY)—yawning longer than 4 seconds, *Tongue Flicking* (T)—normal, rapid protrusions of the tongue, *Writhing Tongue* (WT)—prolonged writhing movements of the tongue, *Chewing* (CHEW)—alternate raising and lowering of the right and left jaw maxilla, *Gulars* (GUL)—the temporary expansion of the throat as in burping Other behaviors measured in minutes included *Climbing* (C)—time spent reared vertically on the aquarium wall, and *Activity* (A)—the time spent actively moving on the floor or along the walls of the aquarium

Statistical Analyses

A repeated measures ANOVA was used to test for "observer" effects and, "drug" effects were calculated using the snake by drug mean square as the error Analyses were applied to square root-transformed data for FG, Y, CHEW, A and GUL Pairwise comparisons of means were conducted only if the appropriate ANOVA F-test was significant (Fisher's protected least significant difference procedure) In analyses in which the percentage occurrence of a given oral behavior among total induced oral behaviors (normal tongue flicks not included) were assessed, arcsin-transformed data for FG and Y were used

RESULTS

Almost no involuntary oral behaviors (G, FG, Y, FY, CHEW, GUL, WT) were observed following the administration of porcine mucin with drug vehicle or when porcine mucin was interacted with 0 05 or 0 5 μg/g HAL, so, those data were neither included in the ANOVA nor in Table 1 However, all treatments involving frog mucus, with or without HAL, induced orofacial behaviors (Table 1) and altered T, C and A (Table 2) Here, the repeated measures ANOVA was applied to all data and tests for drug and mucus main effects and a drug by mucus interaction were performed

No observer effects were apparent when Observer was tested against Snake within Observer interactions

Although HAL did not alter the G, FY, GUL, or WT behaviors induced by frog mucus, both doses of HAL given prior to frog mucus application greatly attenuated mucus-induced FG but greatly potentiated Y CHEW was also significantly potentiated by both doses of HAL While 0 05 and 0 5 HAL were not significantly different in behaviors potentiated/attenuated when interacted with frog mucus, a suggestive dose-related pattern was observed in G, Y and CHEW behaviors

Xenopus mucus significantly reduced normal tongue flicking (T) and the time spent active (A), but significantly increased the time spent climbing (C), a new observation not previously reported in a similar study with snakes (2) (see Table 2) However, neither dose of HAL significantly altered these behaviors when interacted with mucin or frog mucus

To test for any shift in rank of the 7 orofacial behaviors induced by frog mucus alone or in combination with HAL, the mean percentage of each behavior was calculated by taking the total number of induced oral behaviors (normal tongue flicks not included) and dividing it into the total for each induced behavior (Table 3)

When orofacial behaviors are compared by rank of occurrence across treatments, three results are noteworthy First, regardless of treatment, G, WT, GUL and FY retained their same rank CHEW shifted from 6th for mucus only to 4th when mucus was paired

TABLE 2

EFFECTS OF ORALLY APPLIED PORCINE MUCIN (PM) OR SKIN MUCUS (SM) ALONE (0) OR WITH 0 05 OR 0 5 μg/g BODY WEIGHT HALOPERIDOL ON MEAN NUMBER OF NORMAL TONGUE FLICKS (T) AND THE MEAN MINUTES SPENT CLIMBING (C) AND ACTIVE (A)

Behavior	PM0	PM0 05	PM0 5	SM0	SM0 05	SM0 5	S E	SMF	HF	MHF
T (#)	373 0	368 3	477 8	300 1	266 8	295 5	36 9	15 5*	1 87†	1 2†
C (min)	2 5	5 3	8 7	28 5	26 9	26 2	2 3	134 1*	0 36†	1 7†
A (min)	30 9	27 5	28 6	14 3	15 1	15 5	10 1	72 9*	0 20†	0 6†

*Highly significant skin mucus (SM) effect ($p<0$ 0006)

†No significant haloperidol (H) or mucus-haloperidol (MH) effect, pair-wise comparisons among means were not carried out because the haloperidol main effect and interaction were not significant

SMF = F value for the skin mucus effect, HF = F value for the haloperidol effect, MHF = F value for frog mucus-haloperidol effect

with either dose of HAL, but that shift is suggestive (Pr>F = 0 0895) rather than significant G was the highest ranking (2nd) oral behavior to resist a shift in percentage occurrence following either dose of HAL Second, FG ranked first when only mucus was administered but it shifted to 6th and 5th place, respectively, when 0 05 and 0 5 μg/g HAL were administered prior to mucus application Thus, both doses of HAL significantly attenuated the FG induced by frog mucus Third, Y shifted from 4th (mucus only) to the top ranking behavior regardless of the dose of HAL, consequently, HAL significantly potentiated mucus-induced yawning

DISCUSSION

These experiments confirm earlier observations (2) that *Xenopus* granular gland mucus induces involuntary orofacial movements in *N. sipedon* that are similar to those induced in humans (1, 8, 11) and animals (10, 12, 15, 24, 32) given HAL and other neuroleptics HAL administered with sham mucin neither induced oral behaviors nor altered normal T, C or A However, both doses of HAL markedly and consistently attenuated the FG and potentiated the Y and CHEW induced by frog mucus But, G, FY, GUL and WT were not affected by the mucus-HAL interaction The consistency of the replicated data both within and between subjects, and regardless of the dose of HAL, strongly suggests that the observations are not artifacts unique to one or two snakes or to a given dose of HAL Indeed, HAL significantly modulated three of the seven orofacial behaviors induced by *Xenopus* mucus Perhaps most significant is the equivalent shift in the number of FG attenuated and Y potentiated when HAL was administered with frog mucus That stable numerical shift between FG and Y is compatible with the overall constancy of the mean total number of orofacial movements induced per session regardless of the dose of HAL, e.g , mucus only = 120 7, mucus and 0.05 HAL = 124 1, mucus and 0.5 HAL = 143 1 (Table 1)

The mucus-induced orofacial behaviors are not associated with disgust or taste aversions. *Nerodia* never rejected intact, "toxin-loaded" *Xenopus* after previous sessions in which the snakes yawned and gaped uncontrollably nor within a session just following a frog's escape (2)

As HAL is a D2 dopamine receptor blocker, a parsimonious explanation for the mucus-HAL interactions is that Y, FG and CHEW are governed by the snakes' D2 receptors or that the doses of HAL used may have more closely matched the threshold necessary to affect Y, FG and CHEW but not GUL, FY, G or WT However, D1 and D2 receptors may interact in complex ways that promote or attenuate perioral movements, yawning, climbing and rearing in laboratory animals and perhaps reflect the causative mechanism underlying tardive dyskinesia in humans [(6) review, (27)] Thus, future studies must demonstrate how D1 and D2

TABLE 3

MEAN PERCENTAGE OCCURRENCE* OF EACH OROFACIAL BEHAVIOR OBSERVED WHEN *XENOPUS* SKIN MUCUS WAS GIVEN ALONE OR TOGETHER WITH 0 05 OR 0 5 μg/g BODY WEIGHT HALOPERIDOL

Behavior	Mucus and Vehicle	Mucus and 0 05 HAL	Mucus and 0 5 HAL	1 S E	F	$p>F$
Fix Gape‡	12 0 (1)§	1 0 (6)	1 0 (5)	0 02	81 2	0 0001†
Yawning‡	1 0 (4)	13 0 (1)	15 0 (1)	0 02	48 6	0 0001†
Chewing	1 0 (6)	2 0 (4)	2 1 (4)	0 44	3 1	0 0895
Gaping	10 0 (2)	10 0 (2)	12 2 (2)	1 16	1 2	0 3367
Writhing Tongue	6 0 (3)	4 5 (3)	4 2 (3)	0 57	1 5	0 2726
Gular	1 0 (5)	2 0 (5)	1 0 (6)	0 33	2 1	0 1750
Fix Yawn	0 1 (7)	0 2 (7)	0 2 (7)	0 09	0 7	0 5402

*Percentage occurrence = total of oral behaviors from all treatments minus total number of normal tongue flicks, divided into the number of each oral behavior elicited × 100

†Highly significant shift in rank between mucus only and mucus with HAL

‡Arcsin-transformed data

§Numerical rank (1 through 7) of an oral behavior is in parentheses

agonists and antagonists affect the mucus-induced dyskinesias seen in *Nerodia*

Theories that account for neuroleptic-induced movement disorders are all based on mammalian models, therefore, an interpretation of the proximate neural causes in snakes may appear more than speculative However, four observations in this study suggest that the mucus-induced dyskinesias in snakes are remarkably similar to those in mammalian species tested Even the chemistry of *Xenopus'* skin mucus is compatible with mechanisms believed to underlie human movement disorders (2) First, each oral behavior induced in snakes fits by definition those reported in mammals (9, 24–26, 31) Further, drug-induced oral movements in rats occur as intermittent "bursts" (25) or "fits" (30), the precise temporal pattern of behavior observed in this and a previous study using snakes (2) Second, *Xenopus* skin mucus contains peptides [cholecystokinin octapeptide (CCK-8), xenopsin, caerulein (CER), thyrotropin-releasing hormone] and indoleamines (serotonin, bufotenidine) all of which are known to target dopamine and/or serotonin pathways and the tuberoinfundibular axis that controls the release of peptides [e g , prolactin (PRL), adrenocorticotropin (ACTH), α-melanocyte stimulating hormone (α-MSH)] all known to induce yawning [see (2)] Indeed, the neuroleptic effects of CCK-8 and CER as ceruletide have been tested clinically on schizophrenics (17,23) Third, schizophrenics with tardive dyskinesia that were administered ceruletide often exhibited extremely heightened orofacial dyskinesia within the first hours following administration, but this was followed by the disappearance of all dyskinesia for at least three weeks (16, 20, 21) Thus, CER, the structural and functionally more potent analogue of CCK-8 (33), and which occurs in concentrations of 950 μg/g of wet dorsal skin of *Xenopus* (7), is already receiving consideration in studies on human tardive dyskinesia Fourth, the reptilian brain possesses a well defined substantia nigra (a key site in mammalian movement disorders) which is richly endowed with both dopaminergic (29) and serotonergic pathways (22)

The climbing induced by *Xenopus* mucus is unexpected because dopamine agonists induce cage climbing/rearing in mice (18) while dopamine antagonists such as CER and CCK-8, both abundant in *Xenopus* mucus, inhibit climbing/rearing (19,33) However, the normal climbing of arboreal snakes is accompanied by cardiovascular facilitative movements (CFMs) of the body that occur in bouts which proceed anteriorly and independent of normal locomotor movements, they augment blood flow to the heart and brain (14) CFMs have been induced by confining an arboreal snake to a head-up position or by administering hypotensive drugs (13) In the present experiment, mucus-treated snakes typically climbed to the top of the cage and remained motionless without CFMs except for intermittent bouts of oral movements These observations suggest that mucus-induced climbing may be the snake's attempt to behaviorally lower its blood pressure rather than to raise or support it In fact, an early study (9) demonstrated potent sympathomimetic actions of fresh *Xenopus* mucus on heart and blood vessels of the rabbit and cat Recent studies have shown that nearly all of the known active components in *Xenopus* skin mucus are hypertensogenic (3, 5, 28) Further, the neuroleptic properties of both the skin peptides and indoleamines are known to promote the release of PRL, ACTH and α-MSH, all of which induce yawning [see (2)] and elevate blood pressure in rats (4,31) If hypertension-induced climbing in *Nerodia* is confirmed using established methods (13,14), another unique antipredatory strategy (besides dyskinesia-induced escape) may be available to *Xenopus* Here, climbing would reduce successive attacks by snakes (following release via dyskinesia) by "evicting" snakes from *Xenopus'* totally aquatic habitat During the seminal study in which *Xenopus* was fed to *Nerodia* (2), significant cage climbing was observed while snakes held frogs following an attack and after a frog's escape, however, those data were not reported Since then, Zielinski and Barthalmus (34) have observed mucus-induced climbing and oral dyskinesia in the water snake, *Lycodonomorphus rufulus,* a snake known to eat *Xenopus* in Africa In both studies snakes typically remained motionless while vertical on the aquarium wall during intervals between a frog's escape and the snake's initiation of a renewed attack Thus, as wild *Xenopus* never leave the water, the induction of climbing in snake predators may compel snakes to temporarily leave the water

Presently, D1 receptor antagonists are being examined to determine the role of D1 receptors in mucus-induced oral and climbing behaviors

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