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Stimulation of blowfly feeding behavior by octopaminergic drugs

(*Phormia regina*/formamidines/clonidine/hyperphagia)

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ABSTRACT **Adult blowflies (*Phormia regina* Meigen) injected with the octopaminergic drug demethylchlordimeform (10 μg per fly) exhibited enhanced proboscis extension responses when their tarsae were touched to water or aqueous sucrose. They drank more water than saline-injected control flies did but the quantity imbibed was within the normal fluid intake capacity. They became grossly hyperphagic when offered 1 M sucrose, doubling (and in some cases even tripling) their initial body weights. Three other drugs enhanced tarsal responsiveness and induced hyperphagia: DL-octopamine, clonidine (which is known to stimulate octopaminergic receptors in insects), and pargyline, a monoamine oxidase inhibitor. Yohimbine, an antagonist of one class of octopaminergic receptor in insects, prevented the hyperphagia induced by all four drugs. Dopamine, 5-hydroxytryptamine, and DL-norepinephrine failed to cause hyperphagia. These results suggest that octopaminergic receptors in the nervous system of the blowfly positively modulate feeding and drinking behavior.**

In attempting to understand the neural and chemical mechanisms by which insect feeding behavior might be regulated, we injected neuroactive drugs into hungry adult blowflies (*Phormia regina* Meigen) and observed subsequent feeding behavior. *P. regina* was chosen for our studies because a great deal is known about its responses to food stimuli and its food consumption behavior (1). We focused on two components of feeding activity: (*i*) responsiveness to food stimuli as indicated by proboscis extension when the tarsi of the fly were touched to dilute sucrose solutions and (*ii*) actual consumption of 1 M sucrose, a strong stimulus to feeding. Our results demonstrate that blowfly feeding behavior can be manipulated by specific drugs and suggest that receptors of an octopaminergic type may be involved in the regulation of feeding and drinking in these insects.

MATERIALS AND METHODS

P. regina larvae were reared on liver; emerging adults were held for 2 days with water available ad lib but without food. Unless otherwise noted, food-deprived adults were tested on the third day of adult life, and males and females were used indiscriminately (2).

One hour prior to determination of fluid intake, flies were anesthetized with CO_2, weighed, and affixed to a 15-cm length of applicator stick by a droplet of warm wax applied to the dorsum of the thorax. Food consumption was estimated by holding groups of 10 flies with their tarsi in contact with 1 M sucrose or water in such a way that they could extend their mouthparts and imbibe the solution. Flies (plus attached sticks) were weighed to the nearest mg (Cahn DTL electrobalance, Cerritos, CA) shortly before presentation of the solution to be imbibed. The flies were allowed to imbibe the solution for 30 min and then were reweighed. The data obtained enabled us to calculate the amount of 1 M sucrose or water consumed by each fly. Unless otherwise noted, drugs were dissolved in 145 mM NaCl and injected into the hemocoel in a volume of 1 μl. Control flies were injected with saline alone. An Instrument Specialties model M microapplicator (Lincoln, NB) and a 0.25-ml glass syringe fitted with a 30-gauge hypodermic needle were used to inject the drug solutions.

The following drugs were obtained from Sigma: propranolol hydrochloride, pargyline hydrochloride, yohimbine hydrochloride, tranylcypromine hydrochloride, harmaline hydrochloride, and iproniazid phosphate. The other drugs were gifts: clonidine hydrochloride from Boehringer Ingelheim (Ridgefield, CT); clorgyline hydrochloride from May and Baker (Dagenham, Essex, United Kingdom); (−)-deprenyl from J. Knoll (Semmelweis University, Budapest, Hungary); demethylchlordimeform hydrochloride (DCDM) from R. M. Hollingworth (Purdue University); and phentolamine hydrochloride from CIBA Pharmaceutical.

Tarsal responsiveness to sucrose was estimated as the mean acceptance threshold (MAT), the concentration of aqueous sucrose to which 50% of a population of blowflies would respond with full proboscis extension. MATs were estimated by the up-and-down technique described by Thomson (3). In brief, serial 1:2 dilutions of aqueous sucrose were prepared, beginning with 1 M sucrose and ranging down to 0.244 mM. Approximately 100 mounted flies were used in each test. There were three rules for the procedure: (*i*) only flies unresponsive to water were tested on sucrose solutions; (*ii*) each fly was tested only once; and (*iii*) the response of a fly tested on a given dilution of sucrose determined the concentration at which the next fly was tested—i.e., if positive, the subsequent fly was tested on the next more dilute sucrose solution but if negative, it was tested on the next more concentrated one. The concentration used for the first fly in a series was chosen at random. MATs were calculated from the cumulative responses by the weighted-mean procedure recommended by Wetherill (4).

RESULTS

Unrestrained DCDM-treated flies (10 μg per fly) were unable to right themselves for a few minutes after injection with the drug (Fig. 1). Within about 10 min, however, nearly all individuals regained their upright posture. Subsequently their behavior did not deviate greatly from that of saline-injected controls. They walked normally, occasionally took spontaneous flight, and probed the substrate with their proboscis. However, they were somewhat more active than control flies and tended to lose their balance easily after a flight. Some discoordination was evident in that they required a longer period of time to

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Abbreviations: DCDM, demethylchlordimeform; MAT, mean acceptance threshold; MAO, monoamine oxidase.

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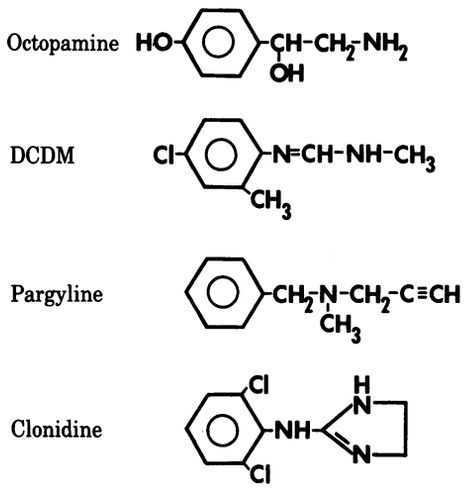

FIG. 1. Drugs that cause hyperphagia and enhanced responsiveness when injected into the hemocoel of adult *P. regina*.

right themselves after falling on their backs than did controls. Thus, except for the first few minutes after injection, DCDM-treated flies were not grossly abnormal in their overall behavior. The effects of clonidine (20 μg per fly) on general behavior were similar to those of DCDM. Pargyline (10 μg per fly) had distinct effects on posture and locomotion. Immediately after injection the flies usually defecated, suggesting a stimulatory action for this drug (5). Within minutes of injection the flies' movements became sluggish, and some unrestrained individuals were unable to right themselves. Discoordination continued for several hours. Increased mortality was observed beginning 12–24 hr after injection with DCDM or pargyline. Clonidine caused no increased mortality within 24 hr.

When the tarsi of flies treated with DCDM, clonidine, or pargyline were touched to sucrose solutions or water, the insects responded by repeatedly extending their proboscises and would drink if allowed to do so. They were markedly more responsive than the controls both to sucrose solutions and to water in the tarsal taste test (Table 1). Individual flies would sometimes respond with proboscis extension when their tarsi were subjected to weak mechanical stimuli.

When flies treated with DCDM, clonidine, or pargyline were offered 1 M sucrose at various times after injection they consumed 2 or more times as much as saline-injected controls (Table 2). Drug-treated flies commonly doubled and occasionally tripled their body weights. Due to the large volume of 1 M sucrose ingested, the fluid pressure in some individuals became extremely high. Such flies were unable to retract their proboscises or ovipositors, and the intersegmental membranes of the abdomen became extremely distended (Fig. 2). Abnormally high consumption of 1 M sucrose would occur if the flies were fed immediately after injection or even if as much as 5 hr

Table 1. Effects of octopaminergic agents on MAT to aqueous sucrose by 3-day-old adult blowflies in a typical experiment

Drug (dose per fly)	MAT, mM*
Saline (1 μl)	13.0
DCDM (10 μg)	<0.25†
Clonidine (20 μg)	0.5†
Pargyline (10 μg)	<0.5†
DL-Octopamine (75 μg)	3.0‡

* At least 100 flies were used for each estimate.
† $P < 0.001$ for difference from control by χ^2 test (6).
‡ $P < 0.02$.

Table 2. Consumption of water and 1 M sucrose during a 30-min period by control and drug-treated adult blowflies

Drug (dose per fly)	Weight increase (mg) after 30-min consumption of	
	1 M sucrose	Water
Saline (1 μl)	13.4 ± 4.6	1.5 ± 2.1
DCDM (10 μg)	49.5 ± 12.2*	12.8 ± 9.6*
Clonidine (20 μg)	41.3 ± 10.5*	11.4 ± 9.3*
Pargyline (10 μg)	47.4 ± 11.4*	14.3 ± 10.3*

Presentation of the 1 M sucrose began 45 min after injection. Values represent the mean (±SD) weight of 1 M sucrose imbibed per fly by a group of 100 flies.
* Significantly greater than control (saline injection) consumption, $P < 0.001$, Student's t test.

passed between injection of any of the drugs and presentation of the sucrose solution (Fig. 3).

In view of the heightened sensitivity to both 1 M sucrose and water of flies treated with any of the three drugs, we sought to determine whether the drugs would also induce increased consumption of water. Flies injected with DCDM, clonidine, or pargyline consumed much more water than saline-injected controls did. The total weight of water imbibed was relatively small, however, averaging about one-third of the mean (±SD) fly body weight of 39.9 ± 4.8 mg (n = 1,000) (Table 2). Because the average drug-treated fly doubled its body weight when allowed to feed upon 1 M sucrose, we believe that it is acceptable to characterize this most prominent effect of the drugs as hyperphagia (7).

We next sought to determine whether DCDM, pargyline, and clonidine would induce hyperphagia in sated as well as in hungry flies. Groups of untreated flies were first allowed to feed to repletion on 1 M sucrose, and the amounts consumed were measured. The flies were then injected with either DCDM (10 μg per fly), pargyline (10 μg per fly), clonidine (20 μg per fly), or saline (1 μl per fly). Forty-five minutes later they were presented with 1 M sucrose a second time. The sated, drug-treated flies imbibed amounts of sucrose even greater than they

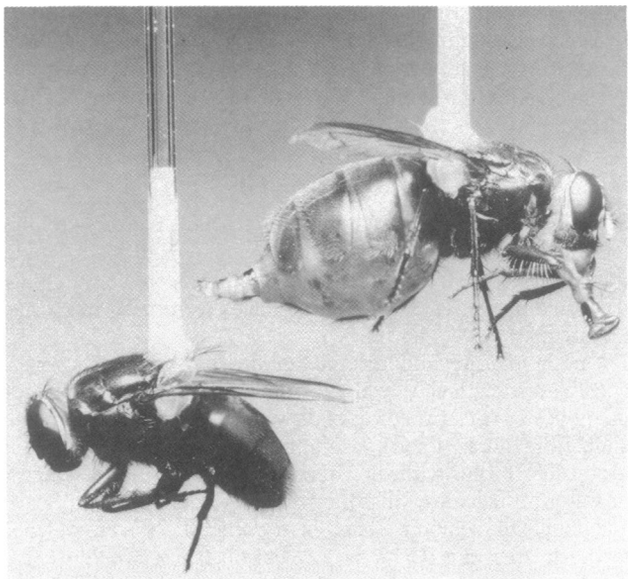

FIG. 2. Drug-induced hyperphagia in the blowfly *P. regina* Meigen. The fly on the left was injected with 1 μl of 145 mM NaCl, held 45 min, and then allowed access to 1 M sucrose for 30 min. During this period, it fed to repletion. The fly on the right was given 10 μg of pargyline but otherwise was treated like the control.

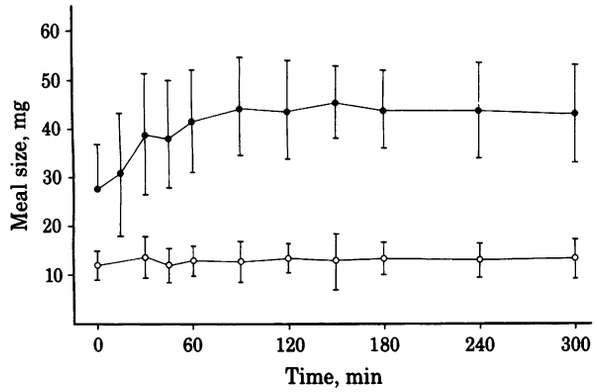

FIG. 3. Consumption of 1 M sucrose by hungry 3-day-old adult blowflies injected with either 1 μl of saline (○) or 10 μg of pargyline (●). The flies were given access to 1 M sucrose for a 30-min period beginning at various times after injection. Each time point represents the mean (± SD) weight of 1 M sucrose consumed per fly. Fifty flies were used for each data point. Curves determined for DCDM (10 μg per fly) and clonidine (20 μg per fly) closely resembled the curve for pargyline.

had during the first feeding period (Table 3). The sated, saline-injected control flies imbibed much less.

Dose–response experiments indicated that hyperphagia could be produced by doses of the drugs lower than those used in most of the other experiments (Fig. 4). The minimal doses of DCDM, clonidine, and pargyline necessary to cause hyperphagia (meal size at least double that of controls) were 2.5, 15, and 7.5 μg per fly, respectively.

One explanation for some of the actions of the three hyperphagia-inducing drugs might be local anesthesia. Such anesthesia could block sensory feedback from the crop via the recurrent nerve. In a normal fly this feedback serves to shut down feeding via an action in the central nervous system (8). Under this hypothesis, we expected to be able to mimic the hyperphagic effect of the three drugs by injecting local anesthetics. But procaine (10 μg per fly), holocaine (10 μg per fly), and lidocaine (10 μg per fly) either failed to cause hyperphagia or caused only a slight increase in meal size (Table 4). Injection of the anesthetics was followed immediately by a state of torpor lasting up to 1 hr. By 1 hr after injection, all individuals had recovered the ability to right themselves and were able to move about normally. Tarsal responsiveness to sucrose after recovery from the effects of anesthesia was similar to that of saline-injected controls.

Pargyline is a well-known propargylamine monoamine oxidase (MAO) inhibitor (9). We sought to determine whether other propargylamine MAO inhibitors would induce hyperphagia.

Table 3. Consumption of 1 M sucrose during a 30-min period by hungry and replete adult blowflies injected with either drug solution or saline

Initial consumption, mg	Injection with (dose per fly)	Consumption after injection, mg
15.3 ± 5.8	Saline (1 μl)	0.2 ± 2.7
14.8 ± 4.7	DCDM (10 μg)	34.5 ± 11.2*
15.6 ± 5.8	Clonidine (20 μg)	27.9 ± 10.6*
15.1 ± 5.5	Pargyline (10 μg)	31.9 ± 10.9*

The flies of each group were first allowed to feed to repletion (30 min) on 1 M sucrose. They then were injected with 1 μl of saline or drug solution. The second presentation of 1 M sucrose began 45 min after the injection. Values represent the mean (±SD) weight of 1 M sucrose imbibed per fly by a group of 50 flies.

* Significantly greater than initial consumption, $P < 0.001$, Student's t test.

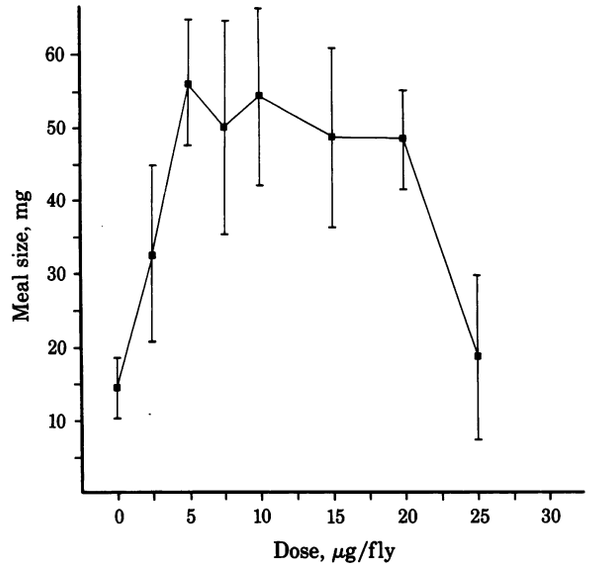

FIG. 4. Consumption of 1 M sucrose after various doses of DCDM. The flies were given access to 1 M sucrose for a 30-min period beginning 45 min after the injection of 1 μl of saline or various doses of DCDM. Vertical axis shows the mean consumption of 1 M sucrose in mg per fly, 50 flies per dose. Vertical lines at each point represent ±1 SD. Dose–response curves for pargyline and clonidine were similar in shape although each was shifted to the right relative to that for DCDM.

Clorgyline and (−)-deprenyl, specific inhibitors of types A and B MAO, respectively, in mammals (10), failed to induce hyperphagia at 10 μg per fly. Clorgyline caused sluggish behavior immediately after injection and significantly decreased consumption of 1 M sucrose. (−)-Deprenyl caused sluggish behavior after a 30-min delay and produced highly variable sucrose consumption. Tranylcypromine, a cyclopropane-type MAO inhibitor, slightly depressed consumption of 1 M sucrose. Harmaline and iproniazid, alkaloid and hydrazine MAO inhibitors, respectively, caused small but significant increases in meal size.

Four additional compounds with potential actions on octopaminergic receptors were evaluated for effects on blowfly meal size: the α_2-adrenergic antagonist yohimbine (11); the preferential α_1-adrenergic antagonist phentolamine (12); the β-adrenergic antagonist propranolol (12); and DL-octopamine. Yohimbine (10 μg per fly in 2 μl) significantly decreased 1 M sucrose consumption when administered alone and prevented the hyperphagic effects of DCDM, clonidine, and pargyline when given together with them (Table 4). Neither phentolamine (10 μg per fly) nor propranolol (10 μg per fly) was effective in preventing the hyperphagia evoked by DCDM, clonidine, or pargyline. DL-Octopamine caused hyperphagia, but the dose required to elicit it was very large. The catecholamines dopamine and norepinephrine and the indolealkylamine serotonin injected at the same high dose did not cause hyperphagia but instead decreased consumption. DL-Octopamine-induced hyperphagia was prevented by concomitant administration of yohimbine (10 μg per fly). In the tarsal taste test, DL-octopamine (75 μg per fly) caused increased responsiveness, although less than that of DCDM, clonidine, and pargyline (Table 1).

DISCUSSION

Feeding activity in blowflies is extremely intense in individuals subjected to concomitant recurrent nerve and ventral nerve cord section, operations that deprive the head ganglia of inhibitory feedback from the crop and abdomen (8). Such flies feed vigorously and almost continuously, lifting their probos-

Table 4. Effects of drugs on the consumption of 1 M sucrose by hungry 3-day-old adult blowflies

Drug (dose per fly)	n	Sucrose imbibed, mg
Saline (1 μl)	700	15.6 ± 5.9
DCDM (10 μg)	260	48.6 ± 14.7*
Clonidine (20 μg)	320	43.7 ± 12.0*
Pargyline (10 μg)	820	46.8 ± 11.9*
DL-Octopamine (75 μg)	40	23.5 ± 6.8*
DL-Octopamine (100 μg)	60	31.9 ± 8.5*
Clorgyline (7.5 μg)	180	3.8 ± 4.5*
(−)-Deprenyl (10 μg)	80	17.6 ± 18.3
Harmaline (10 μg)	100	23.9 ± 9.5*
Tranylcypromine (10 μg)	110	11.1 ± 4.5*
Iproniazid (10 μg)	100	20.4 ± 6.1*
Yohimbine (10 μg)	190	8.5 ± 6.0*
Phentolamine (10 μg)	160	15.6 ± 5.5
Propranolol (10 μg)	130	15.7 ± 5.8
Yohimbine + DCDM (10 μg each)	160	1.8 ± 3.3*
Yohimbine + clonidine (10 μg, 20 μg)	170	3.5 ± 5.7*
Yohimbine + pargyline (10 μg each)	190	5.4 ± 5.5*
Phentolamine + DCDM (10 μg)	150	49.2 ± 11.4*
Phentolamine + clonidine (10 μg, 20 μg)	160	44.2 ± 11.4*
Phentolamine + pargyline (10 μg each)	230	47.2 ± 14.7*
Propranolol + DCDM (10 μg each)	160	46.0 ± 12.6*
Propranolol + clonidine (10 μg, 20 μg)	110	44.6 ± 14.4*
Propranolol + pargyline (10 μg each)	120	45.8 ± 13.6*
Holocaine (10 μg)	60	19.1 ± 5.6*
Lidocaine (10 μg)	70	10.1 ± 6.7*
Procaine (10 μg)	50	14.6 ± 9.9
Dopamine (100 μg)	50	7.5 ± 3.5*
5-Hydroxytryptamine (50 μg)	40	8.8 ± 5.2*
DL-Norepinephrine (100 μg)	40	6.4 ± 3.3*

Drugs were administered in 1 μl of saline injected 45 min prior to presentation of 1 M sucrose for 30 min. Values are mean (±SD) weight increase per fly.
*Significantly different from control, $P < 0.001$.

cises from the food only occasionally and briefly. The abnormal feeding behavior that follows injection of DCDM, clonidine, or pargyline fits this description closely: feeding is almost continuous, with only occasional and transient lifting of the proboscis from the aqueous sucrose. The similarities between the behavioral effects of double nerve sectioning and of DCDM, clonidine, and pargyline injection suggest that they may have a common mode or site of action. Gelperin (13) has explained the intense feeding behavior that follows double nerve section by postulating that inhibitory information from the foregut and abdominal stretch receptors is additive in the central nervous system. It may be that drug-induced hyperphagia results from suppression of incoming inhibitory sensory feedback information within the central nervous system. A simple hypothesis to account for this suppression would be that the drugs inhibit or negatively modulate the postsynaptic elements upon which the two types of stretch receptor inputs coverage. This would effectively silence negative feedback from the stretch receptors, and hyperphagia would result.

An alternative explanation for the similarities between hyperphagic behavior induced by double nerve section and by the three drugs is that local anesthesia is involved in the actions of the drugs. Under this hypothesis, information flow in the recurrent nerve and the ventral nerve cord would diminish or cease altogether because the drugs block axonal conduction. The feedback inhibition to the brain from the stretch receptors of the crop and abdominal wall would thus be interrupted as effectively as if the nerves had been sectioned. However, three local anesthetics—procaine, holocaine, and lidocaine—did not cause hyperphagia and did not mimic the effects on feeding or other behavior seen with DCDM, clonidine, or pargyline. A second problem with the local anesthesia hypothesis is that it is difficult to reconcile with the dramatic increases in tarsal responsiveness seen in flies treated with DCDM, clonidine, or pargyline. Drugs with local anesthetic action would be expected to attenuate incoming sensory information and reduce tarsal responsiveness rather than enhance it.

It seems unlikely that DCDM, clonidine, or pargyline owe their hyperphagic effects to MAO inhibition. Although pargyline is a MAO inhibitor and DCDM inhibits MAO moderately (14), there is little evidence that MAO is important in the metabolism of aromatic biogenic amines in insect nervous tissues (15). Further, other potent MAO inhibitors failed to affect meal size, reduced it, or caused only a small increase. In those cases in which small increases occurred (iproniazid and harmaline), this effect might easily have arisen via actions not involving MAO, such as direct receptor stimulation.

A simple hypothesis to explain the hyperphagia that follows hemocoel injection of DCDM, clonidine, pargyline, and DL-octopamine is that receptors of an octopaminergic type normally modulate feeding behavior in the central nervous system of adult *P. regina*. Activation of these receptors by the four drugs promotes the increase in meal size. Several types of evidence support this hypothesis. First, Dethier and Gelperin's experiments with double nerve section point toward a central nervous system site for the control of meal size (8, 13). The similarities between the effects of double nerve section and those of the hyperphagia-inducing drugs are consistent with a central, and common, site of action for the drugs and the nerve projections. Additional support for a central nervous site of action for DCDM, clonidine, pargyline, and DL-octopamine in *P. regina* comes from recent observations that injection of octopamine directly into the protocerebrum of honeybees causes increased responsiveness to water vapor as well as food odor. Other aromatic biogenic amines failed to produce this effect (16).

Second, clonidine is an agonist of α-type adrenergic receptors in mammals (17) and of one type of octopaminergic receptor in the locust (18). DCDM likewise is an agonist of octopaminergic receptors in the firefly (19) and the locust (20). Pargyline is not known to be a receptor agonist, yet its structural similarity to the aromatic biogenic amines (Fig. 1), the reported amphetamine-like action of certain propargylamines (5), and the known potency of pargyline in inhibiting mammalian MAO are consistent with specific interactions with octopaminergic or other types of aromatic biogenic amine receptors.

Third, octopamine, dopamine, and serotonin occur in the brain and nerve cord of insects (15, 21, 22), where they evidently serve as chemical messengers.

Fourth, yohimbine, an antagonist of α_2-adrenergic receptors in mammals (11) and octopamine$_1$ receptors in locust myogenic muscle fibers (18), prevents the hyperphagic effect of DCDM, clonidine, pargyline, and DL-octopamine. The failure of propranolol and phentolamine to block the drug-induced hyperphagia suggests that specific receptors mediating the hyperphagic effect are either not blocked by these two adrenergic antagonists or that they fail to attain sufficient concentration in the vicinity of the receptors to produce blockade.

Although it may appear that the drug-induced increase in water consumption by blowflies is relatively greater than the drug-induced increase in sucrose consumption, this impression may result from the experimental design. The experiments were performed with well-hydrated, although starving, flies. Their

base-line intake of water was low, as would be expected, whereas their base-line sucrose consumption was high. Thus, when water and sucrose imbibition before and after drug treatment are compared, the disparity in the base-line consumptions gives a misleading impression as to which parameter changed most extensively. We believe that net percentage gain in total body weight provides a better basis for comparison. Viewed in this manner, sucrose consumption is at least twice as great as water intake. Additionally, sucrose consumption by drug-treated flies was extraordinary: it is clear that they consumed 1 M sucrose to the extreme limits of bodily capacity. Water intake, on the other hand, never exceeded the volume of a normal meal and thus ceased well before the limits of fluid intake capacity were approached.

Special attention needs to be given to the point that DL-octopamine itself causes hyperphagia. The dose needed was extremely high (≈2,000 μg per g of fly weight). However, DL-octopamine-induced hyperphagia seems not to be merely a nonspecific effect resulting from the massive dose because dopamine, serotonin, or DL-norepinephrine given in very high doses did not cause hyperphagia. Indeed, flies treated with high doses of these drugs displayed decreased consumption. The need for extremely high doses of DL-octopamine to evoke hyperphagia is presumably related to poor penetration of positively charged DL-octopamine through the insect blood/brain barrier into the central nervous system (23). Positively charged ions penetrate into insect ganglia more slowly than do neutral or negatively charged species (24); cations such as methylene blue may not penetrate at all into the neuropile. Electron microscopic studies of the penetration of lanthanum ions into the central ganglia of a closely related species of blowfly, *Calliphora erythrocephala*, support the existence of a blood/brain barrier in adult blowflies (25). In addition to physical retardation of entry, there may be a chemical barrier against octopamine: it may be subject to *N*-acetylation by a potent *N*-acetyltransferase in insect nervous tissue (26).

Although low in comparison to DL-octopamine, the doses of DCDM, clonidine, or pargyline needed to cause hyperphagia in the blowfly still appear to be relatively high (60–300 μg per g of fly weight). However, it should be remembered that these seemingly high doses were used to evoke maximal sucrose consumption. It is clear (Fig. 4) that smaller, but still measurable, increases in meal size would result from much smaller doses of the drugs.

While not as striking as massive hyperphagia, the large increase in tarsal responsiveness in flies injected with DCDM, clonidine, or pargyline is also remarkable, especially in view of its occurrence in flies starved since emergence and thus already having low tarsal thresholds. It is of interest to consider the relationship between hyperphagia and hyperresponsiveness. Blowflies made hyperphagic by the surgical procedures discussed above fail to show the increase in threshold that normally follows a meal (8). Examination of the effects of this surgery on responsiveness prior to feeding appears not to have been attempted. By arguments similar to those used earlier, we suggest that receptors of an octopaminergic type, presumably located in the central nervous system of the blowfly, positively modulate sensory inputs from sugar and water and possibly even mechanosensory receptors in the tarsi and labellum. Several of our observations are consistent with this hypothesis: (*i*) DCDM, clonidine, pargyline, and DL-octopamine increased tarsal responsiveness to aqueous sucrose; (*ii*) drug-treated flies responded to water more frequently than did control flies; (*iii*) mechanical stimulation of the tarsi of drug-treated flies often caused proboscis extension. Positive modulation of responses to incoming sensory stimuli by drugs is suggestive of "central excitatory state" (27); it may be that the octopaminergic receptors mediate the central excitatory state, thereby decreasing the threshold.

The behavioral effects of DCDM, clonidine, and pargyline can by summarized as positive modulation of feeding behavior because the drugs promote the initiation of feeding and prolong its duration. We speculate that these octopaminergic agonists owe their effects to interaction with octopaminergic receptors that are normally involved in the regulation of feeding behavior, probably in the central nervous system of the fly.

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