

Taste Reactivity Analysis of 6-Hydroxydopamine-Induced Aphagia: Implications for Arousal and Anhedonia Hypotheses of Dopamine Function

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The deficits in feeding and drinking that result from 6-hydroxydopamine (6-OHDA) lesions of the mesostriatal dopamine system are often explained using either sensorimotor arousal or anhedonia hypotheses. Sensorimotor arousal hypotheses posit that dopamine systems facilitate the capacity of sensory stimuli to activate any motor output. The anhedonia hypothesis suggests that dopamine systems amplify the hedonic impact of positive reinforcers. Natural palatability-dependent ingestive and aversive actions, which are emitted by rats to tastes, provide a sensitive test that can discriminate between these hypotheses: A reduction of sensorimotor arousal should diminish the ability of tastes to elicit any actions, whereas anhedonia should shift the balance between positive and aversive actions. To directly compare these two hypotheses, taste reactivity was examined in rats made aphagic by intranigral 6-OHDA injections. The results did not support either of these predictions: Taste reactivity was essentially unchanged. The persistence of normal taste reactivity argues against both an anhedonia and a global sensorimotor arousal interpretation and provides further evidence that the capacity for hedonics can be neurologically dissociated from motivated appetitive behavior. An incentive attribution hypothesis that can account for the results is discussed, along with its implications for a wide range of phenomena associated with dopamine depletion.

The aphagia and adipsia produced by selective destruction of mesostriatal dopamine-containing neurons, and the milder motivational deficits that accompany pharmacological blockade of this system, have been the focus of intense investigation for the past 20 years (e.g., Fibiger, Zis, & McGeer, 1973; Marshall, Richardson, & Teitelbaum, 1974; Oltmans & Harvey, 1972; Smith, 1976; Stricker & Zigmond, 1976; Ungerstedt, 1970, 1971; White, 1986; Wise, Spindler, de Wit, & Gerber, 1978). Advanced originally as an alternative to hypothalamic cell loss as a cause for the lateral hypothalamic syndrome (Ungerstedt, 1970, 1971), loss of the system of neurons that originates in the substantia nigra and ventral tegmentum, and ascends to targets primarily in the striatum (Björklund & Lindvall, 1984) is now generally recognized to be one of a number of separate ways by which discrete brain lesions can abolish feeding and drinking (e.g., Grossman, 1979; White, 1986).

The psychological nature of the deficit underlying 6-hydroxydopamine- (6-OHDA) induced aphagia remains controversial, but many competing hypotheses have tended to fall into one of two categories. The first category arose from observations that dopamine depletion produces many general or, at least, noningestive deficits: for example, failures to orient to somatosensory or visual stimuli, to spontaneously initiate natural behavior of diverse sorts, and to properly control the form of locomotion patterns or posture (Marshall,

Turner, & Teitelbaum, 1971; Schallert et al., 1982; Schallert, Whishaw, DeRyck, & Teitelbaum, 1978; Ungerstedt, 1971; White, 1986). This category of hypothesis suggests that ascending dopamine systems modulate either sensorimotor responsiveness (e.g., White, 1986), meaning the ability of sensory stimuli to engage motor response systems, or a nonspecific arousal factor (Stricker & Zigmond, 1976, 1978, 1986) that is affected by many stimuli and that activates all behavior in an essentially Hebbian (Hebb, 1955) fashion. By this view, damage to the mesostriatal dopamine system reduces the "normal activating properties of exteroceptive sensory stimuli and thereby diminishes behavioral activity" (Stricker & Zigmond, 1986, p. 689). The same suppression of response activation may apply even more strongly to interoceptive stimuli, according to this hypothesis (Stricker & Zigmond, 1986, pp. 685-686). A consequence is that dopamine-depleted animals cannot respond at all to weak sensory stimuli (Stricker & Zigmond, 1976). Furthermore, if arousal or responsiveness factors facilitate response generation to suprathreshold stimuli in a constant or linear fashion, these animals would be expected to show a reduced response even to stronger stimuli. This view is supported by experiments demonstrating that activation of intact ascending catecholamine systems by amphetamine or apomorphine increases activity and the tendency of animals to approach objects (Iversen, 1977) and sensitizes the motor startle response to loud noise (Kokkinidis, 1984). The behavioral elicitation effects produced by electrical stimulation of ascending dopamine neurons also has been interpreted in terms of regulation of sensorimotor responsiveness (Valenstein, 1976).

The second category of explanation emphasizes a more specific motivational process that might be mediated by do-

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pamine systems. In the anhedonia hypothesis (Gray & Wise, 1980; Wise, 1978, 1982, 1985; Wise et al., 1978), Wise formulated and refined an idea that had been developing since the early investigations by Olds and Travis (1960) on chlorpromazine and reinforcement. This hypothesis asserts that ascending dopamine systems mediate the *hedonic* properties of natural reinforcers such as food, as well as of artificial reinforcers such as brain stimulation or catecholamine agonists including amphetamine or cocaine. In states of dopamine deficiency, "all of life's pleasures—the pleasures of primary reinforcement and the pleasures of their associated stimuli—lose their ability to arouse the animal" (Wise, 1982, p. 52). This anhedonia hypothesis can account for many of the effects of dopamine antagonists that elude explanation by global arousal, motor deficit, or simple sensorimotor hypotheses. These effects include interactions between neuroleptic administration and experience with the reward in situations ranging from response acquisition to extinction, spontaneous recovery, and resistance to extinction (Wise, 1982). For example, the disruption of instrumental responding for food or electrical brain stimulation by low doses of neuroleptics develops only gradually and after repeated exposures to the food, producing an extinction-like response curve (Fouriez, Hansson, & Wise, 1978; Fouriez & Wise, 1976) that is associatively specific to the extinguished context (Gallistel, Boytim, Gomita, & Klebanoff, 1982). Perhaps even more powerful support for the anhedonia hypothesis has come from the curve-shift brain stimulation paradigm of Edmonds and Gallistel (1974). This procedure, which examines response rate at a variety of reinforcer intensities, is affected differently by manipulations of reward strength versus of response capacity and can therefore discriminate the effects of reward decrement from those of motor impairment. Manipulations that impair the ability of the animal to perform a response, such as increasing the force required for execution or administering low doses of the paralytic curare, produce one pattern of results. Manipulations likely to entail reward decrements, such as reduction of the number of stimulation pulses per train, produce a different pattern (Edmonds & Gallistel, 1974; Gallistel, Shizgal, & Yeomans, 1981; Stellar & Stellar, 1985). Low doses of neuroleptic drugs produce behavioral changes consistent with reward reduction rather than motor impairment alone (Gallistel et al., 1982; Stellar, Kelley, & Corbett, 1983; Wise, 1985).

Both the sensorimotor arousal and the anhedonia hypotheses command strong empirical support, but neither can fully account for the phenomena that the other was invented to explain. It follows that either (a) both types of psychological function are embedded within mesostriatal dopamine systems or else (b) the true role of ascending dopamine projections is crucial to both motivational and sensorimotor function but is not well described by either hypothesis at present. If the latter is true, then a new hypothesis is needed.

Our inability to dismiss either existing hypothesis in favor of the other has meant that it is impossible to account conclusively for why aphagia and adipsia result from dopamine lesions or blockade. There are too many potential reasons to choose from. A reduction in ingestive behavior would be predicted to follow impairment of sensorimotor responsive-

ness or arousal. But it would also be expected to follow impairment of hedonic processing or of any of the other functions that have been suggested, such as oromotor control, homeostatic monitoring, and so forth. We cannot assign responsibility for aphagia to the failure of any one psychological function. The difficulty arises in part because the chief measure of ingestive behavior, amount consumed, is affected similarly by very different psychological and neural manipulations (Rowland, 1980).

The taste reactivity test developed by Grill and Norgren (1978a) provides a measure that can discriminate between at least the two broad classes of hypotheses described earlier. Richly patterned natural responses are emitted by rats in reaction to oral infusions of taste solutions. The responses are organized temporally and by correlation into two main groups that correspond respectively to the hedonic intensity of the positive and negative assessments of taste palatability (Grill & Berridge, 1985). Positive and aversive assessments are essentially independent decisions (Berridge & Grill, 1983, 1984), and each may be affected differently by changes in taste composition (e.g., Grill & Norgren, 1978a), the physiological state of the rat (e.g., Berridge, Flynn, Schulkin, & Grill, 1984; Grill & Norgren, 1978c), and by pharmacological (e.g., Berridge & Treit, 1986), neurological (e.g., Grill & Norgren, 1978b), and associative (e.g., Grill & Norgren, 1978c) manipulations that would be expected to alter perceived taste palatability. At the same time, each natural action is a facial or somatic motor response elicited by a sensory stimulus in a predictable and controlled fashion (Berridge & Fentress, 1986).

The dual nature of taste reactivity components as indicators of palatability assessments and as sensory triggered motor responses means that they can be affected both by hedonic (Grill & Berridge, 1985) and by sensorimotor factors (Berridge & Fentress, 1986). But, unlike measures of intake, they are affected by each in different ways. Manipulations that alter the hedonic perception of food palatability can be recognized on the basis of taste reactivity. Aversion may be enhanced, as occurs after taste aversion conditioning (Grill & Norgren, 1978c), or after electrolytic lateral hypothalamic (Fluharty & Grill, 1981; Schallert & Wishaw, 1978), or neurotoxic-induced globus pallidus (Berridge, Fentress, & Treit, 1988) lesions. Alternatively, aversive responses can be held constant, whereas positive palatability is manipulated either incrementally, as by chlordiazepoxide administration (Berridge & Treit, 1986), or decrementally, as by trigeminal deafferentation (Berridge & Fentress, 1985).

If dopamine depletion produces anhedonia, that is, a reduction in the hedonic impact of primary food stimuli, then 6-OHDA lesions of ascending dopamine systems should selectively reduce positive responses. The anhedonia hypothesis could be rephrased to allow it to cover both limbs of the affective response by positing global hedonic evaluation to depend on the balance between positive and aversive assessments. This revision would allow the hypothesis to accommodate aphagia produced through an enhancement of aversion as well as through a reduction in positive palatability.

In contrast, a reduction either of simple sensorimotor re-

sponsiveness or of a general arousal factor that activates all behavior would be expected to nonspecifically reduce all responses, without regard to palatability. Sensorimotor reactivity of taste-elicited components has been shown to conform to the predictions of an activation model that operates by a probabilistic rate parameter set by stimulus intensity (Berridge & Fentress, 1986). This parameter determines both the likelihood that any of a particular action will be emitted by a rat and the actual number of actions it will emit, if it emits any. If dopamine depletion produces a general reduction in sensorimotor arousal, then there should be a decrement in this parameter, and, therefore, a reduction in both the number of rats showing a particular response to a given taste concentration (i.e., an elevation of threshold), and a reduction in the mean number of responses emitted by an individual rat (i.e., a suppression of sensorimotor gain).

This experiment was designed to test these two alternative predictions.

Method

Subjects

Thirty-six male Sprague-Dawley rats were housed in group cages with ad-lib access to food and water. Twenty-six rats were assigned to the 6-OHDA lesion group, and 10 rats to the surgical control group. They were kept on a 14:10-hr light/dark cycle. All surgery and testing was performed during the light portion of the cycle.

Surgery

A common method of protecting cells containing norepinephrine from damage induced by 6-OHDA is to pretreat with desipramine or a similar norepinephrine re-uptake blocker (Breese & Traylor, 1971). However, these drugs also have gastrointestinal effects, which involve abdominal distension and reduced intestinal food absorption (Koob, Riley, Smith, & Robbins, 1978; Saller & Stricker, 1978). Gastrointestinal distress could influence feeding and food hedonics either directly or by association with food to produce conditioned aversions. To control for this possibility, both the control and experimental groups of rats were subdivided equally into those that either did or did not receive desipramine (20 mg/kg, ip) 30 min before surgery. Rats were anesthetized with ketamine (100 mg/kg, im) and acepromazine (1 mg/kg, im). They also received bicillin (30,000 units, im) and atropine sulfate (1 mg/kg, ip) before surgery.

The 6-hydroxydopamine HBr (2.0 $\mu\text{g}/\mu\text{l}$) was dissolved in cold 0.9% sterile saline-ascorbate (0.1 mg/ml) solution and kept on ice. With bregma and lambda in the same horizontal plane, bilateral skull holes were drilled 5.0 mm posterior to bregma and 2.0 mm lateral to midline, and the dura was opened. A 30-ga. stainless steel cannula was lowered into the rostral zona compacta of the substantia nigra (7.3 mm ventral to dura) and, after 1 min, 4 μl of the 6-OHDA solution was infused at a constant rate by syringe pump over 10 min. The needle was left in place an additional 2 min after the injection. Control rats received intranigral injections of the saline-ascorbate solution using the same procedure.

At the same time, bilateral chronic oral cannulas were implanted in all rats to allow later infusions of taste solutions into the mouth. These cannulas (heat-flared PE 100 tubing) entered the mouth lateral to the first maxillary molar. They ascended lateral to the skull and exited dorsally, where they were attached to 19-ga. steel tubing and anchored with skull screws and acrylic cement.

Postsurgical Maintenance

All rats were allowed free access to regular chow pellets and water and also to commercial baby cereal mixed with water to form a loose mash. In addition, they were intubated with 10 ml of water twice on the day after surgery to prevent dehydration. Thereafter, rats that lost weight were intubated each day with 10 ml of a liquid diet (sweetened condensed milk mixed equally with water plus vitamins) for every 5 g of weight lost, up to three intubations per day.

Rats were classified as aphagic if they ate neither chow nor mash throughout the period of testing and received all their calories by intubation. Rats that never ate chow pellets during testing but did eat some cereal mash were classified as *hypophagic*. Rats that ate any chow pellets were classified as *nonaphagic*.

Behavioral Testing

Testing began 3 days after surgery. Each rat received one taste reactivity trial per day for 10 consecutive days using eight different taste solutions. The first two solutions were repeated on the last 2 days of testing, but aside from this, solutions were administered in random order. Solutions were chosen to reflect a range of taste palatability and intensity: sucrose (0.03 and 1.0 M), NaCl (0.15 and 0.5 M), HCl (0.01 and 0.1 M), and quinine HCl (3×10^{-3} and 3×10^{-4} M). Tests began at least 2 hr after intubation if a rat was being tube fed.

For each trial, a rat's oral cannulas were connected to stimulus delivery tubes (PE 50 with PE 10 nozzles), and the rat was placed in a cylindrical test chamber to habituate for 5 min. A mirror was located beneath the transparent floor at an angle to reflect an image of the rat's face and mouth into the zoom lens of a videocamera. One ml of the taste solution was then infused via cannulas into the mouth at a rate of 1 ml/min, and the behavior of the rat was videotaped for later analysis.

Behavioral Analysis

The frequency of occurrence of specific actions was ascertained by slow motion (frame-by-frame to $1/10$ normal speed) inspection of the videotaped record by an observer blind to the experimental condition of the rat. Ingestive responses scored were (a) paw licking; (b) lateral tongue protrusions (nonrhythmic) past the lip followed by forward extension, lasting approximately 165 ms; and (c) rhythmic tongue protrusions along the midline with a total cycle length of 165 ms. A weakly ingestive or neutral action was rhythmic mouth movement without tongue protrusion at the same or lower frequency as rhythmic tongue protrusions. A neutral or weakly aversive behavior was passive drip, that is, the passive leaking of fluid from the mouth. Strongly aversive actions scored were (a) gapes—large opening of the jaw with retraction of the lips, lasting approximately 125 ms; (b) chin rubbing—bringing the chin into contact with the floor while projecting the body forward; (c) face washing—either a single wipe with the paws or a bout of several wipes; (d) forelimb flails—shaking of the forelimb at greater than 60 Hz; (e) paw treading—planting of the forelimbs on the floor and alternating forceful strokes forward and back; and (f) rapid locomotion about the chamber (see Grill & Berridge, 1985; Grill & Norgren, 1978a, for the classification of these actions).

For the purpose of quantifying the number of responses emitted, discrete actions such as lateral tongue protrusions, gapes, chin rubs, and bouts of face washing, forelimb flailing, and locomotion were recorded each time they occurred. Continuous actions that typically persist for seconds were recorded as follows: paw licks, mouth movements, and passive dripping were recorded in 5-s bins (any occur-

rence of these actions up to 5-s duration was scored as a single occurrence). Rhythmic tongue protrusions were scored in the same way, but in 2-s bins.

Neurochemistry

Eight of the most severely aphagic rats from the 6-OHDA group (4 that received desipramine, 4 that did not) and 4 rats from the control group were used for biochemical analysis. The rats were killed by decapitation, and their brains were removed from the skull and cooled in iced saline within 40 s of death. After cooling for 1 min, the brain was placed on a chilled cutting block, and slices of brain were removed as described by Heffner, Hartman, and Versteeg (1980). The left and right striatum were extracted with a micropunch, pooled, weighed, and placed in tubes containing 400 μ l of 0.05 N HClO₄ with dihydroxybenzylamine (250 ng/10 μ l) added as an internal standard. The tissue was homogenized, and the suspension was centrifuged for 45 min at 5,000 \times g. The supernatant was filtered through 0.45- μ m pore filters. The samples were frozen at -20 °C for no more than 2 weeks before being assayed for dopamine, dopamine metabolites, and 5-hydroxyindoleacetic acid by high performance liquid chromatography with electrochemical detection (Robinson, Becker, Young, Akil, & Casteñeda, 1987).

Results

Spontaneous Feeding

Control rats began eating food pellets by the second day after surgery. Of the rats that received 6-OHDA, 11 were severely aphagic for periods ranging from 8 to 30 days. Fifteen 6-OHDA rats were initially hypophagic (eating only wet cereal), and 6 of these began eating food pellets before the end of testing. There was no difference in aphagia between rats that had or had not received desipramine.

Neurochemistry

The mean (\pm SE) striatal dopamine concentration for control rats was 17.74 \pm 1.43 ng/mg wet tissue weight, and for the 8 most aphagic 6-OHDA-treated rats, it was 2.61 \pm 1.69 ng/mg, which is 14.7% of the control value (range = 6%–29% of control value).

Ingestive/Aversive Consummatory Response Categories

Both control and 6-OHDA-treated rats showed predominantly ingestive responses to sucrose or dilute NaCl, mixed ingestive and aversive responses to HCl or concentrated NaCl, and predominantly aversive responses to quinine. The number of combined ingestive responses (paw licking, lateral tongue protrusions, and tongue protrusions) did not vary between rats that had received desipramine and rats that had not, $F(1, 34) < 1$. Similarly, the number of combined aversive responses (gapes, face washing, forelimb flails, chin rubbing, and paw treading) was unaffected by desipramine, $F(1, 34) < 1$. Desipramine and nondesipramine groups were therefore combined for all further analyses.

The mean number of combined ingestive responses elicited by each taste stimulus was unaffected by whether the rats belonged to the aphagic, hypophagic, or control conditions,

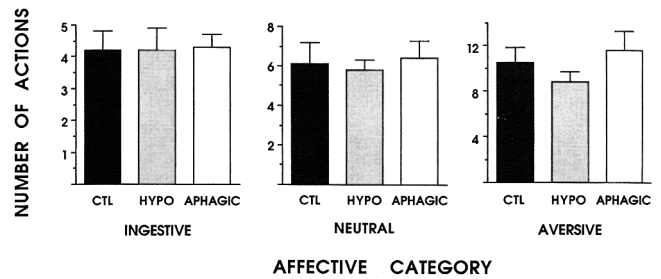


Figure 1. Mean (\pm SE) number of combined ingestive actions (paw licks, lateral tongue protrusions, rhythmic midline tongue protrusions), neutral actions (mouth movement and passive dripping), and aversive actions (gapes, head shakes, face washes, forelimb flails, chin rubs and paw treads) shown per trial by control (CTL) rats, and by hypophagic (HYPO) and aphagic groups of 6-hydroxydopamine treated rats. (Responses to the eight separate taste solutions have been collapsed together.)

$F(2, 33) < 1$ (Figure 1). The nature of the taste stimulus, however, was a powerful determinant of the number of ingestive responses for all rats, $F(7, 231) = 16.50$, $p < .001$, as mentioned earlier (Figure 2); there was no interaction between taste and aphagia conditions, $F(14, 231) < 1$.

Similarly, the mean number of combined aversive responses elicited by each taste was equivalent across control, hypophagic, and aphagic conditions, $F(2, 33) < 1$. Aversive responses were affected only by taste stimulus, $F(7, 231) = 6.93$, $p < .001$. There was again no interaction between taste stimulus and aphagic conditions, $F(14, 231) < 1$.

Within-Category Consummatory Response Pattern

A more fine-grained analysis was conducted to ascertain whether mesostriatal dopamine depletion altered the distribution of specific actions (e.g., paw licks, tongue protrusions, etc.) within the larger affective categories (i.e., ingestive, neutral, or aversive). Figure 2 depicts the number of each action shown by control and aphagic 6-OHDA rats to the highest concentration of each taste. There were no significant differences in terms of action number, but a separate analysis of the number of rats showing each action (response incidence) did indicate that ingestive responses may be slightly redistributed among the rhythmic tongue protrusion and lateral tongue protrusion action categories. Aphagic rats showed a lower incidence of rhythmic midline tongue protrusions to sucrose and NaCl solutions than did controls, but a higher incidence of nonrhythmic lateral tongue protrusions ($p < .05$ each; z test of proportions). Deficits in midline tongue extension are produced by lesions of a variety of forebrain structures, including the lateral hypothalamus (Levine & Schwartzbaum, 1973; Whishaw, Kolb, & Sutherland, 1983).

Thresholds of Responsiveness

The failure of dopamine depletion to reduce the average number of ingestive and aversive responses elicited by taste stimuli argues against a simple global sensorimotor arousal hypothesis, assuming that ascending dopamine systems am-

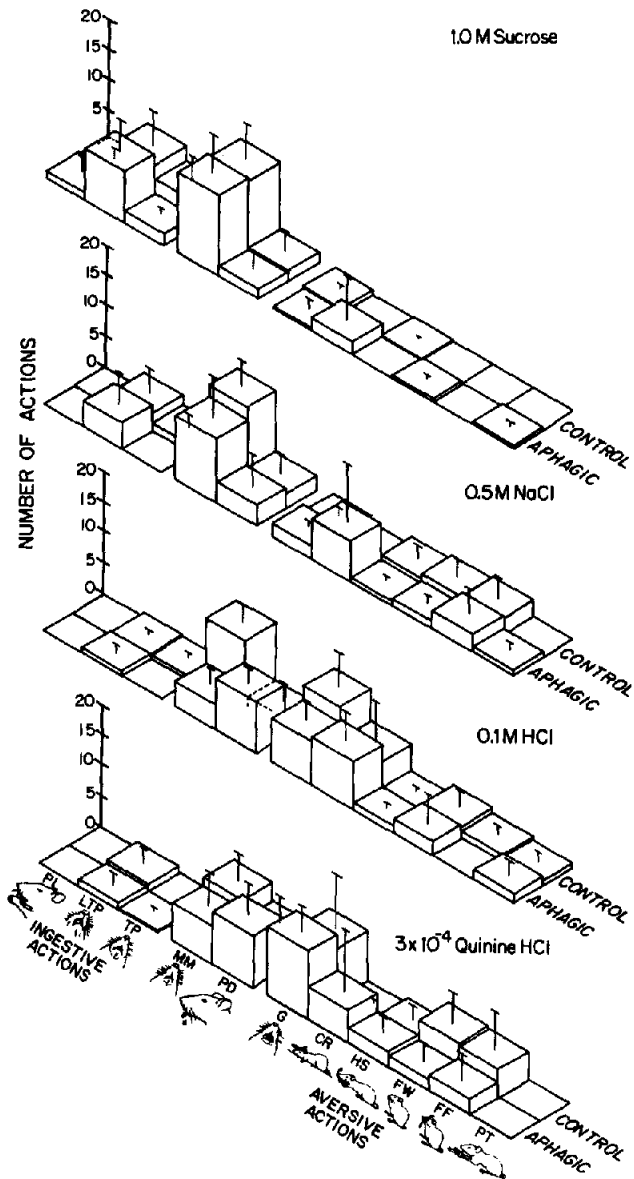


Figure 2. Taste-elicited action components ($M \pm SE$) elicited by the highest concentrations of each stimulus in control and aphagic 6-OHDA groups. (PL = paw lick; LTP = lateral tongue protrusion; TP = rhythmic tongue protrusion; MM = mouth movement; PD = passive drip; G = gape; CR = chin rub; FW = face wash; FF = forelimb flail; HS = headshake; PT = paw tread.)

plify linearly the ability of any sensory stimulus to evoke a response. Response systems may respond to changes in stimulus intensity in a variety of nonlinear ways, however (cf. Berridge & Fentress, 1986, regarding taste-elicited responses), and sensorimotor arousal theories of dopamine function have generally been most explicit about response thresholds at low levels of stimulus intensity. More specifically, low-level stimuli are held to be less likely to elicit a response (e.g., Stricker & Zigmond, 1978; White, 1986), and it is conceivable that this could be true even if the response at higher levels of stimulation was not altered. One way of

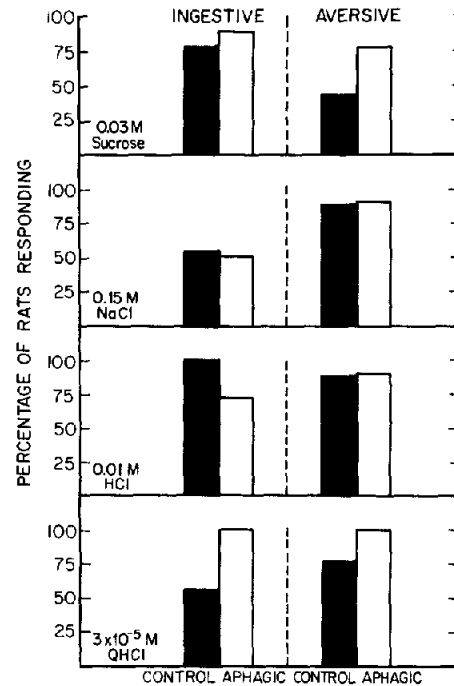


Figure 3. Response incidence to weak stimuli. (Percentage of rats in the control and aphagic 6-hydroxydopamine groups that showed ingestive or aversive responses to the lowest concentrations of each taste stimulus.)

testing the proposition that dopamine-depleted rats are less likely to respond at low-stimulus intensities is to ascertain the percentage of individuals that respond at all to weak stimuli, that is, stimuli that evoke responses in fewer than 100% of normal rats. Such stimuli are below threshold for at least some control individuals, and an increase in threshold would be expected to reduce further the percentage of individuals showing responses (Berridge & Fentress, 1986). Comparison of the actions elicited by the lower concentrations of all four taste stimuli used in the present study provides a test of these predictions. Figure 3 illustrates that the percentage of individuals showing ingestive or aversive responses to low-intensity taste stimuli was the same in 6-OHDA aphagic and control groups. Note that this measure is one of response likelihood rather than response intensity. The failure of dopamine depletion to affect this incidence measure indicates that damage to mesostriatal dopamine projections does not make rats less likely to respond to weak taste stimuli.

Discussion

Dopamine depletion produced by 6-OHDA lesions of the substantia nigra resulted in severe aphagia but failed to alter ingestive and aversive consummatory actions elicited by oral infusions of taste stimuli. These results provide strong evidence against a straightforward interpretation of either the sensorimotor arousal or anhedonia hypothesis of dopamine function. If ascending mesostriatal systems increased the likelihood of responding to low-stimulus intensities via threshold modulation, and if aphagia resulted from this im-

paired capacity to respond to mild stimuli, then dopamine-depleted aphagic rats ought to have had a lower incidence of individuals showing ingestive and aversive responses to weak taste stimuli (and possibly also a reduced number of all elicited responses even at higher stimulus intensities if mesostriatal systems also increased the amplitude of all stimulus-elicited responses). But neither the incidence nor the total number of ingestive/aversive responses were diminished in aphagic 6-OHDA rats. On the other hand, if aphagia occurs because dopamine depletion blocks or attenuates the hedonic impact of primary reinforcers such as food, and if palatability-dependent consummatory responses indicate the hedonic impact of tastes, then aphagic 6-OHDA rats ought to have shown a selective reduction in ingestive reactions (if dopamine affects positive hedonics only) or a reduction in ingestive reactions coupled to an increase in aversive reactions (if dopamine regulation of hedonia involved modulation of both positive and aversive subsystems). But aphagic 6-OHDA rats showed normal numbers of total ingestive and aversive responses, and their responses were appropriate to the taste they received. This does not rule out the possibility that more extensive dopamine depletion might produce a change in taste reactivity (see Schallert, 1985), but it does demonstrate that aphagia produced by 6-OHDA lesions can occur without any such change. These results suggest that both the sensorimotor-arousal or anhedonia hypotheses must be revised to exclude predictions about some types of behavior, or they must be replaced by an hypothesis that can account for these data. A number of potential revisions and replacements are considered below.

Reflexes Versus Integrated Behavior

Both the anhedonia and sensorimotor hypotheses were formulated largely to explain disruption of complex, integrated behavior such as instrumental performance, obtaining and ingesting food to meet homeostatic requirements, and so forth. One might wish to exempt taste-elicited consummatory actions from predictions the hypotheses generate on the grounds that such actions are reflexes, in that they follow simple stimulus-response rules that require little integration and because their basic forms are generated by brain-stem mechanisms (Grill & Norgren, 1978b). But this is not likely to be a valid exemption. These actions do involve complex integration and are greatly influenced by forebrain systems. For one, taste-elicited responses are not generated in a fixed fashion to a given stimulus (if reflex is taken to have such a narrow meaning, as a reflex vs. integrated behavior distinction requires). Rather, taste signals are integrated in a complex way with information from many other sources. Physiological cues regarding energy availability, and hormonal signals involved in calorie, water, and sodium balance, modulate the response elicited by oral sucrose, water, or salt (Berridge et al., 1984; Grill & Miselis, 1981; Grill & Norgren, 1978c). Pavlovian associations with the postingestive consequences of tastes (Berridge, Grill, & Norgren, 1981; Grill & Norgren, 1978c; Pelchat, Grill, Rozin, & Jacobs, 1983; Zellner, Berridge, Grill, & Ternes, 1984), with the other elements of a compound taste (Berridge & Schulkin, in press;

Breslin, Davidson, & Grill, 1987), and with exteroceptive predictors of a taste to follow (Delamater, LoLordo, & Berridge, 1986) are integrated to control the response emitted in the presence of the conditioned stimulus. Such integration can be so powerful as to completely reverse the pattern from entirely ingestive to entirely aversive responses (e.g., Berridge et al., 1981; Grill & Norgren, 1978c), or vice versa (e.g., Zellner et al., 1984). Although taste-elicited consummatory actions are generated by the brain stem, the pattern of action elicited by an oral infusion is strongly determined by forebrain influences. Modulation of ingestive/aversive responses by physiological sodium appetite or associative taste-aversion learning requires forebrain circuitry (Grill & Norgren, 1978c; Grill, Schulkin, & Flynn, 1986). Even the unconditioned response to a novel solution is influenced profoundly by forebrain manipulations such as telencephalic ablation (Grill & Norgren, 1978b), restricted electrolytic lesions of the hypothalamus (Fluharty & Grill, 1981; Schallert & Whishaw, 1978), and excitotoxic lesions of the corpus striatum (Berridge et al., 1988). Taste-elicited consummatory responses cannot be considered to be carried out autonomously by a low level neural circuit or generated in an entirely stereotyped fashion to a given input. The evidence indicates that normal taste reactivity is not a stereotyped reflexive response to sensory stimulation, but rather reflects a complex affective evaluation (positive hedonic and negative aversive), which integrates information from many different sources and which involves the participation of both diencephalic and telencephalic structures in animals that have them (see Grill & Berridge, 1985, for a review).

Qualitative Response Distinctions:

Appetitive-Type I Versus Consummatory-Type II

A second way of accounting for why taste-elicited actions are not affected by dopamine depletion might be to distinguish them from other behavior on the basis of response category rather than response complexity. The early American ethologist Wallace Craig (1918) distinguished between appetitive phases of motivated behavior, which bring an animal into contact with a goal object, and consummatory phases, which are elicited by the goal itself and which consummate the appetitive sequence. This distinction is similar to operant/respondent or instrumental/elicited behavior classifications, and also overlaps partly with the Type I/Type II distinction based on hippocampal and neocortical electroencephalographic correlates (Vanderwolf, 1971, 1975). Taste-elicited actions are consummatory and most likely to be Type II, and many of the instrumental paradigms that gave rise to the anhedonia hypothesis are appetitive and Type I. The approach or postural orientation responses often used in sensorimotor assessment also would qualify sometimes as appetitive-Type I behavior. One might argue, therefore, that only appetitive-instrumental-Type-I behavior requires ascending mesostriatal dopamine systems and that consummatory-elicited-Type II behavior does not. Using this distinction, Blackburn, Phillips, and Fibiger (1987) have shown that doses of pimozide that attenuate conditioned preparatory approaches to a food source signaled by a tone may not

reduce consumption of that food once it is delivered. They suggest that their results indicate a dopamine dependence for preparatory behavior elicited by secondary reinforcers but not for consummatory behavior elicited by primary reinforcers. In terms of sensorimotor responsiveness, support for a preparatory/consummatory distinction comes from observations that bilateral 6-OHDA lesions do not affect flinch or startle elicited by electric shock (Price & Fibiger, 1975; Smith, 1976), whereas anticipatory avoidance of shock is disrupted by such lesions (Fibiger, Phillips, & Zis, 1974; Price & Fibiger, 1975; Smith, 1976).

An appetitive versus consummatory or a Type I versus Type II distinction is more plausible than one based on response complexity. But it also faces difficulties and has limitations. First, the distinction between appetitive and consummatory phases is only one of degree, and there is no absolute defining feature for either category (Hinde, 1953). Second, the distinction does not fit perfectly to the pattern of responses affected by dopamine manipulations. Blackburn et al. (1987) emphasized the relative protection of food consumption from pimozide suppression, but it was effects on consumption by 6-OHDA lesions and neuroleptics that in large part gave rise to the arousal hypothesis of Stricker and Zigmond (1976) and the anhedonia hypothesis of Wise (1978). Of course, even food consumption itself involves an appetitive approach phase by Craig's (1918) original definition. This suggests that the dissociation found by Blackburn et al. (1987) might not be best accounted for on the basis of an appetitive versus consummatory response category distinction (a possibility they recognize). Rather, the dissociation might be between the appetitive response to food itself versus the appetitive response to a signal for food. Further, it should be noted that even responses that have no appetitive phase cannot be asserted to be independent of dopaminergic function. Although flinch thresholds may not be affected by dopamine lesions, as noted earlier, acoustic startle responses are facilitated by dopamine agonists (Kokkinidis, 1984). Similarly, nigrostriatal 6-OHDA lesions do affect the direction and efficacy of stimulus-elicited grooming (Schallert, 1982).

It is difficult to be certain whether an EEG-based Type I versus Type II distinction would fit better than an appetitive/consummatory one without additional data regarding the EEG classification of each behavior measured here. But neither Type I nor Type II EEG patterns are abolished by dopamine depletion (Whishaw, Robinson, Schallert, DeRyck, & Ramirez, 1978), which suggests that dopamine is not required to engage those neural systems responsible for the performance of Type I behavior. On the other hand, dopamine depletion does greatly reduce the probability of occurrence of most Type I actions (e.g., walking, rearing). An interesting exception is one behavior normally classed as Type I, namely, postural adjustment (Vanderwolf, 1971, 1975), which is greatly increased in frequency following dopamine depletion (Whishaw et al., 1978). Although neither this exception nor the objections to an appetitive/consummatory distinction given above rule out response category distinctions as explanations of dopamine function, they do constitute major difficulties that must be dealt with by any revision

based on response category. Finally, it should be noted that even a successful appetitive-consummatory or Type I-Type II response distinction would at best provide an explanation only for those phenomena previously accounted for by sensorimotor arousal hypotheses. It would still be necessary to account in some other way for interactions between neuroleptics and experience with reinforcers (e.g., extinction mimicry, response-reinforcement curve shift, etc; Wise, 1982, 1985) that gave rise to the anhedonia hypothesis.

Incentive Salience Modulation

Even if the effects of dopamine depletion are not fully accounted for by a response category distinction, the distinction might still point the way indirectly to a more complete solution phrased in stimulus-centered terms. Unlike relatively "prewired" consummatory responses, appetitive behavior is to a large degree elicited and guided by configurations of "neutral" stimuli that have become incentives through experience (cf. Bindra, 1978; Toates, 1986). Incentive stimuli not only predict significant events to follow but can also take on new eliciting and reinforcing properties themselves (cf. Toates, 1986), including some of the hedonic properties normally carried by the consummatory stimuli they predict (e.g., Berridge & Schulkin, in press; Delamater et al., 1986; Dickinson & Dearing, 1979).

An implication of this acquisition of affective properties by neutral stimuli is that the perceptual salience and motivational significance of most sensory stimuli is to a large degree actively generated or attributed by the nervous system. It follows that a neural system must exist to readjust and attribute motivational salience to stimuli, and that disruption of this neural system would disrupt motivated behavior even if both the mechanisms that generate the actual motor behavior and that generate primary affect remained intact. (The terms motivational, perceptual, salience, and significance will be deliberately mixed in this account, because the function being suggested shares features with each and could be viewed as a subcomponent of all.) The hypothesis that best accounts for the data may be that mesostriatal dopamine neurons belong to a system that assigns salience or motivational significance to the perception of intrinsically neutral events (see, also, Beninger, 1983; Blackburn et al., 1987; Fibiger & Phillips, 1986). Intrinsically neutral events or objects are those the animal is not biologically predisposed to find salient, aversive, or rewarding. The attribution of salience can be supposed to be required for such events to become attractive and capable of controlling behavior. The significance or salience of these inherently innocuous stimuli becomes assigned and modulated partly by immediate emotional state variables and partly through incentive learning. Incentive learning about the sight and sounds of food, and so forth revalues those sights and sounds in part by creating central associative representations of those events (Mackintosh, 1983; Rescorla, 1987). When those incentive stimuli are encountered again, their associatively gained significance must be reattributed in order from them to effectively control behavior. Dopamine systems might facilitate both the reevaluation and subsequent attribution of salience

to incentive stimuli in these situations, without being required for the formation of associative representations or for the capacity for affect in general.

The idea that mesostriatal dopamine systems are involved in attributing salience to originally neutral stimuli could account for many diverse phenomena. Extinction-like performance under pimozide, the prevention of new conditioned reinforcer development, and curve-shift phenomena (cf. Wise, 1982, 1985) could all result from failures to boost or maintain the salience of incentive stimuli with each rewarded trial. The ability of pimozide to progressively decrease eating rate within a meal without increasing the latency to initiate feeding (Wise & Colle, 1984; Wise & Raptis, 1986) could be understood by presuming that the visual and olfactory incentive stimuli of food elicit each bite, and that they must be continually reenhanced by this neuroleptic-sensitive system in a normal meal. At higher neuroleptic doses or after 6-OHDA lesions, preexisting and even well-established incentive stimuli such as the sight of food might lose their salience, and the initiation of feeding would be affected. Aphagia, adipsia, and so forth would persist until either recovery of function owing to compensatory neural changes occurred or until conditions arose that allowed a nonincentive based reinforcement system to control behavior (Miller & Kessen, 1952).

If we assume that the unconditioned salience of innocuous (but potentially threatening) tactile stimuli produced by a touch to the vibrissae or body must also be actively generated and modulated to some extent, it may be possible to account even for certain 6-OHDA deficits usually considered to be sensorimotor, such as the failure to orient or respond properly to mild somatosensory stimuli (e.g., Marshall et al., 1971; Schallert et al., 1982). Disruption of a neural system that attributes salience (based here in part on nonassociative state factors: e.g., waking vs. sleeping, recent occurrence of an aversive event, etc.) to these stimuli that in themselves have no inherent eliciting features would reduce elicited orientation. Changes in exteroceptively guided locomotion (Pisa & Szechtman, 1986; Wise & Holmes, 1986) produced by dopamine manipulations could also be accounted for in this way (but, see Teitelbaum, Schallert, & Whishaw, 1983, for a discussion of endogenous changes in locomotion). Painful or aversive stimuli, however, which naturally activate their own affect and response systems, would not be impaired in efficiency (Price & Fibiger, 1975; Smith, 1976) just as hedonic and aversive taste reactivity was unimpaired in this study.

Conclusion

According to current theories (Bindra, 1978; Toates, 1986), the creation of new incentives should in principle entail at least three steps: (a) the capacity for biologically significant stimuli to engender affect, (b) the association of affect with originally neutral stimuli, and (c) the attribution of salience or motivational significance to the no longer neutral stimulus when it is next encountered. The results described here indicate that the mesostriatal dopamine system is not required for the hedonic first step, nor does it modulate sensorimotor responsiveness in a global fashion. Similar conclusions have

been reached by Gallistel (1986) on the grounds that mesostriatal systems are not metabolically activated by rewarding lateral hypothalamic stimulation, and by Gallistel and Freyd (1987) on the basis of the form of neuroleptic dose-response curves in a self-stimulation task. They have suggested that dopamine systems mediate the associative second step, memory consolidation (see, also, Beninger, 1983). Formulations in terms of the third step, salience attribution, do not require postulating deficits in learning or memory formation per se, yet could still account for deficits in certain learning tasks. Furthermore, a salience attribution hypothesis has the attraction of accounting also for some sensorimotor changes produced by dopaminergic manipulations. These changes include the hyperresponsiveness to stimuli produced by electrical stimulation (cf. Fibiger & Phillips, 1986; Valenstein, 1976) or pharmacological sensitization (Robinson & Becker, 1986) of the mesostriatal dopamine system and the sensorimotor hyporesponsiveness to innocuous tactile stimuli produced by 6-OHDA lesions (Schallert et al., 1982). Future empirical work may allow us to refine these alternatives further and distinguish more clearly among them.

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