



Effect of Drugs on Catnip (*Nepeta cataria*)-Induced Pleasure Behavior in Cats

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SUMMARY

Cats exposed to stuffed toys sprayed with catnip (*Nepeta cataria*) extract exhibited pleasurable behavior which was divisible into 6 phases and which terminated in approximately 10 minutes. Preadministered drugs which shortened the response included atropine sulfate, physostigmine, neostigmine, pilocarpine, mecamlamine, methysergide, and pentobarbital. Hexamethonium, amphetamine, 5-hydroxytryptophan, atropine plus methysergide, and diphenylhydantoin abolished the response. The effect of diphenylhydantoin took several weeks to disappear. Response was prolonged by morphine, chlorpromazine, and histidine. Atropine methyl nitrate, *N*-(2-chloroethyl)dibenzylamine, propranolol, and chlorpheniramine did not affect duration of response. Most drugs and several environmental, physiologic, and psychologic factors altered the response qualitatively. The results indicated peripheral nicotinic and central muscarinic cholinceptive and serotonergic facilitation of the catnip response, with a prominent voluntary component. Inhibition of response seemingly involved central muscarinic and nicotinic cholinceptive mechanisms linked with an adrenoceptive component. Interrelationships proposed for these components support current concepts of behavior control. The catnip response may be suited to the study of pleasure behavior and olfaction and may be used as a model of human reactions to marijuana and lysergic acid diethylamide (LSD).

Responses of cats exposed to catnip are well known to pet owners and veterinarians. The behavior of cats reacting to catnip is obviously directed toward reward (pleasure). Outdoors, cats will seek the plant after scenting it, and return to it each day to eat and roll in the foliage.

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Man also experiences pleasure sensations from catnip. The dried leaves or the extract, when smoked, produce symptoms similar to those of marijuana and LSD.¹⁴ Visual and auditory hallucinations are part of the catnip, marijuana, and LSD effects in man.¹⁴ In the author's experience, cats also manifest signs of apparent visual or auditory hallucinations while under the influence of catnip.

There are few animal models of pleasure behavior. The catnip response in

cats not only may allow further study of pleasure behavior and olfaction, but may also be a model for the study of mechanisms of human reactions to marijuana and LSD.

The specific purposes in the present study were to determine the effect of single doses of various drugs on duration, character, and intensity of the catnip response and to describe the behavior pattern in more detail. The objectives were to determine whether the response was explainable in terms of brain cell types, locations, and functions, and to discover whether the overall results were consistent with current concepts of behavior control, such as the two-arousal hypothesis,³³ linking mechanisms between limbic components,³⁶ and redundant control mechanisms.^{18,20}

Review of Literature

Catnip, or catmint (*N. cataria*), is a perennial herb belonging in the mint family (Labiatae).⁴ It grows on roadsides and wasteland throughout the upper middle United States and lower Canada. The plant is succulent and has an odor rather like a mixture of mint and fresh cut grass or alfalfa. In the dried plant, the alfalfa-like odor predominates.

The original discovery of catnip's power to attract cats is lost in history. It is well known that the fresh or dried plant, or the juice or extract, causes cats to manifest peculiar, often humorous behavior indicative of extreme pleasure. Catnip can be purchased in pet stores in the dried chopped form, either loose or in small toys. An aerosol can extract is also available for spraying on cat toys in the home.

In 1941,²¹ the ingredients of catnip oil, after steam distillation, were described as 50% nepetalactone, 33% nepetalic acid, and 14% viscous yellow neutral fraction. Nepetalactone could be prepared from nepetalic acid, and nepetalic acid could be prepared from nepetalactone. A year later, these workers²² amended their data to 42% nepetalactone, 36% nepetalic anhydride, 15% β -caryophyllene, 3% ether, and 2% ester. It was found, in tests made using

⁴ Sliife, F. W. (ed.): Weeds of the North Central States. Circular 718, University of Illinois Agricultural Experiment Station, Urbana, Ill. 1960.

lions, that nepetalactone was the constituent responsible for attraction of cats. More complete lists of ingredients of catnip oil are available.^{24,29,30}

Chemically, the terpenoid nepetalactone is the δ -lactone of 2-(2-hydroxy-1-methylvinyl)-5-cyclopentanecarboxylic acid. References are available as to biosynthesis³¹ and chemistry³¹ of the compound. The substance has been analyzed by gas²⁹⁻³¹ and thin layer⁴⁶ chromatography.

The discovery⁵ that nepetalactone exists in 2 isomeric forms (cis, trans, and trans, cis) led to tests in cats in which the trans, cis isomer was found to be the feline attractant form.⁵ Results of a study⁴⁶ of metabolism of nepetalactone in cats given large doses of the chemical by the oral route should be interpreted with care because the wrong isomer of nepetalactone might have been used.

In a study⁴¹ of genetic determination of the catnip response, the behavior pattern was divided in 4 components: (1) sniffing, (2) licking and chewing with head shaking, (3) chin and cheek rubbing, and (4) head-over rolling and body rubbing. Several factors such as age, environment, degree of distress or anger, and unknown factors were found to inhibit or modify the behavior pattern, which was concluded to be heritable as an autosomal dominant. In addition, it was believed⁴¹ that a cat could react to air concentrations of nepetalactone as small as 1 part of 10⁹ to 10¹¹. The similarity of catnip-induced rolling to estrous rolling indicated a relationship of catnip behavior to estrous behavior. In a study²⁵ comparing estrous behavior and catnip-induced behavior patterns, rubbing, rolling, and head shaking were found to be due specifically to the odor of catnip. Estrous behavior was similar to, but not the same as, catnip-induced behavior. Catnip did not cause vulvar presentation, vocalization, or foot treading characteristic of estrus, and cats in estrus did not shake their heads as much as did cats exposed to catnip. Furthermore, the fact that male cats responded to catnip in the same manner as females was acknowledged as "an interesting problem," but was not taken as evidence against a relationship between estrous behavior and the catnip-induced response. Mention was not made of the possibility that catnip may simply produce a natural form of pleasure behavior which is unrelated, or only partly related, to sexual stimulation.

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terpenoid nepetalactone 2-(2-hydroxy-1-methyl-3-carboxylic acid. Reference as to biosynthesis²¹ of the compound. The substance is synthesized by gas²²⁻²⁴ and thin layer chromatography.

Nepetalactone exists in cis, trans, and trans, trans isomers in which the trans, trans isomer is the feline attractant. A study²⁵ of metabolism in cats given large doses orally should be made because the wrong interpretation might have been

made in the determination of the behavior pattern components: (1) sniffing, (2) rolling with head shaking, (3) rubbing, and (4) head rubbing. Several environmental factors were shown to be heritable. In addition, it was suggested that it could react to air as small as the similarity of catnip-induced rolling and head rubbing behavior to that induced by catnip study²⁶ comparing catnip-induced behavior, rolling, and head rubbing due specifically to catnip behavior was the same as, catnip-induced did not cause salivation, or foot rubbing of estrus, and cats rubbed their heads as much as catnip. Furthermore, cats responded to catnip as a "pleasure problem," but was not a relationship between the catnip and the catnip response was not made. Catnip may simply induce pleasure behavior which is partly related,

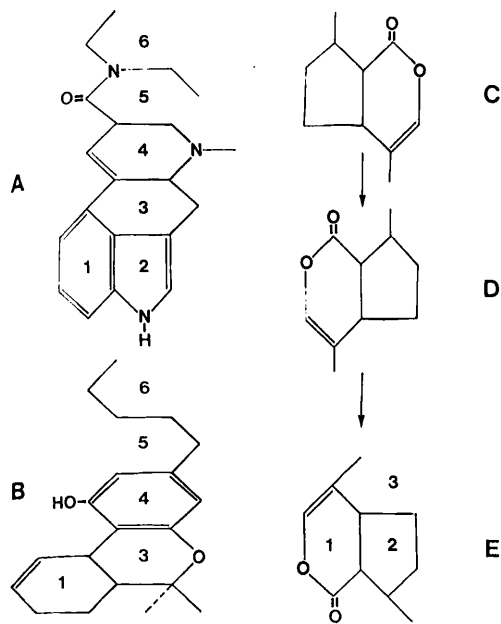


Fig. 1.—Structure of nepetalactone compared with that of lysergic acid diethylamide (LSD) and tetrahydrocannabinol. (A) Structure of LSD with rings numbered 1 through 6. (B) Structure of tetrahydrocannabinol, the psychedelic principle of marijuana, showing similarity to LSD. (C) Structure of nepetalactone, the feline attractant in catnip, as conventionally written. (D) Transposed representation of nepetalactone. (E) Inverted and loosened representation of nepetalactone, showing some characteristics of LSD and tetrahydrocannabinol.

Until the report¹⁴ of marijuana- and LSD-like effects of catnip in man, it was generally recognized that only the Felidae were affected by catnip. It is not known whether nepetalactone is the psychedelic principle in catnip, but its chemical structure is reminiscent of portions of the LSD and tetrahydrocannabinol molecules (Fig. 1). This similarity could be used to predict psychedelic activity of nepetalactone.²⁸

Information could not be found concerning brain mechanisms of catnip-induced pleasure behavior or the effect of drugs on the response.

Materials and Methods

Selection of Cats.—Initially, 17 healthy mixed-breed cats (weighing between 2.5 and 5.0 kg. each) of both sexes, 6 months to several years old, were acclimated to the caged environment. Each cat was exposed to catnip at 2- to 3-day intervals until the

response of the cat became predictable in duration, intensity, and character. Three cats did not respond and were excluded from the study proper, but were retained as satellites to the study to determine whether drug treatments would induce them to react to catnip. Ten cats were allotted at random to the principal group and 4 cats to the control group. As the study proceeded, cats were eliminated or new cats were added to the principals due to the operation of factors which interfered with the behavior pattern.

Experimental Design.—All cats were exposed to catnip in the afternoon of the same day each week. All of the cats were pretreated with 1 ml. of saline solution given intraperitoneally (I.P.) the first week. The principals were pretreated with a different drug or drug combination each week for the ensuing 5 weeks. On the 6th week, the principals were given only saline solution, and this was repeated every 3rd week as an internal control measure. Drugs were given each week between saline solution treatments. Sequence of drug administration was adjusted so that drug interaction from week to week was either unlikely or irrelevant, based on nature of the drug, rate of drug metabolism, and observations made in pilot studies.^b

Data from the principals regarding duration of catnip reactions were analyzed by *t* tests for paired comparisons²⁹ in which the mean from each drug experiment was compared with that of the saline solution experiment of the week before or after. In this way, a saline solution experiment was never more than 1 week removed from any drug experiment, except during the first 4 experiments.

^b Preliminary studies in groups of 2 to 4 cats not previously given drugs indicated the same effect on the catnip response as reported here. Additionally, there were never overt signs of residual drug action week to week in this experiment. Nevertheless, steps taken to counter possible inapparent drug interactions between experiments included: following a drug with an antagonist (e.g., physostigmine after atropine sulfate, atropine methyl nitrate after physostigmine, neostigmine after atropine methyl nitrate, pilocarpine after neostigmine); following a drug with an agent of apparent opposite effect on the catnip reaction (e.g., morphine after amphetamine, chlorpromazine after *N*-(2-chloroethyl)dibenzylamine, histidine after methysergide-atropine sulfate); following a drug with a drug of same primary pharmacologic action (e.g., atropine methyl nitrate after physostigmine-atropine methyl nitrate, hexamethonium after mecamylamine); following a drug with a drug of similar side actions (e.g., chlorpromazine after *N*-(2-chloroethyl)dibenzylamine, chlorpheniramine after propranolol, several others); following drugs of unpredicted interactive capacity with saline solution; and placing at the end of the experiment the drug (diphenhydantoin) most likely to interfere with the effects of other substances.

Exposure and Recording Procedures.—Exposure to catnip was by means of stuffed toys sprayed with the extract.^c The freshly sprayed toy was placed in the cage with the cat. Duration of reaction was measured from introduction of the toy to cessation of response. Intensity of response was arbitrarily graded as 0 = no response; 1.0 = very weak response (sniffing, licking toy briefly, 1 to 2 head shakes, holding toy down with a front paw, crawling of skin over the back, grooming); 2.0 = moderate response (sniffing, licking, several shakes of the head, rubbing toy, clutching toy with extended front claws, biting, rolling on cage floor, grooming); 3.0 = strong response (sniffing, licking, several shakes of the head, rubbing toy, clutching toy with front claws, biting, chewing and shaking toy as if it were a rat, rolling on cage floor, tearing at toy with hind claws, grooming); and 4.0 = augmented response, meaning stronger response than normal for the cat (intensification of a phase or occurrence of frenzy, strong apparent euphoria, affection, or sexual stimulation). All actions of each cat were dictated to an assistant. The response was considered complete when the cat would no longer respond to the toy when the toy was moved or rubbed against the cat. Overall impressions gained from the entire group of cats were recorded after each experiment.

Drug Pretreatments.—Each drug was dissolved in saline solution and injected I.P. 0.5 to 2.5 hours before exposure to catnip.^d The subcutaneous (s.c.) route of injection was used with atropine methylnitrate when that agent was employed to block peripheral muscarinic (*m*) side effects of cholinomimetics. Drug dosages, as the salts, were carefully selected during pilot studies and on basis of reading the literature^{4,10,19,44} to ensure the production of the desired drug effect for the desired duration, but with minimal side effects.

Drugs used as pure substances were: atropine sulfate, physostigmine sulfate, hexamethonium chloride, *l*-histidine HCl, *dl*-5-hydroxytryptophan (5-HTP), and pilo-

^c VIP brand catnip extract, Vo-Toys, Inc., Bronx, New York, N.Y.

^d The entire group of cats was treated; testing commenced when the 1st cats treated manifested obvious signs characteristic of the drug used. With some agents such as atropine, drug action was apparent in 0.5 hour. With others, such as 5-HTP, drug action required more time for onset. No cat was tested unless drug action was prominent or at least 0.5 hour had elapsed since treatment.

carpine nitrate^e; atropine methylnitrate^f; neostigmine methylsulfate^g; mecamlamine HCl^h; *dl*-amphetamine sulfate and *N*-(2-chloroethyl)dibenzylamine HClⁱ; morphine sulfate^j; chlorpromazine HCl^k; propranolol HCl^l; chlorpheniramine maleate^m; methysergide bimalateⁿ; pentobarbital sodium^o; and diphenylhydantoin sodium.^p

Results

Normal Responses to Catnip.—The behavioral pattern observed in most cats after the stuffed toy was placed in the cage could be divided in 6 sequential phases. Phase 1 included immediate alerting, scenting, approaching, and sniffing of the toy, all in rapid order. Phase 2 began as the cat commenced shaking the head, licking the toy, salivating, and rubbing the head against the toy, often while holding the toy in place with a front paw and manifesting a twitching or crawling of the skin over the back. In phase 3, the cat would give up its footing and roll over onto the toy with head down. The front claws were used to clutch the toy in a tight embrace while the cat increased the intensity of rubbing and licking and began biting or chewing the toy. Phase 4 occurred as the cat, still clutching the toy, began kicking the toy with the hind feet, claws extended as if to eviscerate the toy. The cat would often chew the toy or shake it as if it were a rat. Extreme pleasure was indicated by the observed behavior. Rubbing, rolling, stretching, and sometimes very animated leaping about the cage also were seen in phase 4. In phase 5, termination of the reaction was imminent, and the reaction was interrupted by rather urgent grooming activities, as if parts of the

^e Nutritional Biochemicals Corporation, Cleveland, Ohio.

^f Strassenburgh Pharmaceuticals, Rochester, N.Y.

^g Hoffmann-LaRoche, Inc., Nutley, N.J.

^h Merck, Sharp and Dohme, Pest Point, Pa.

ⁱ Smith, Kline and French Laboratories, Philadelphia, Pa.

^j British Drug Houses, Ltd., Toronto, Ont., Canada.

^k Poulenc, Ltd., Montreal, Que., Canada.

^l Ayerst Laboratories, New York, N.Y.

^m Schering Corporation, Bloomfield, N.J.

ⁿ Sandoz Pharmaceuticals, Hanover, N.J.

^o Bell-Craig Pharmaceutical Company, Toronto, Ont., Canada.

^p Sigma Chemical Company, St. Louis, Mo.

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body were itching. The cat usually licked the genital region, the paws and legs, and the shoulders or thorax. This activity was interspersed with more phase 1, 2, 3, or 4 activity of brief duration. Phase 6 occurred when the cat rather suddenly abandoned the toy, either walking away from it, sitting and watching the observer, or lying down near or upon the toy.

Signs of apparent hallucinations (phantom "butterflies" above the cat, phantom "mice" in the cage) or sexual stimulation (erection in males, estrous stance with vocalization, vulvar presentation, and treading of hind feet in females, or "love-biting" of the proffered hand by both sexes) were occasionally seen. The apparent hallucinations and penile erections were spontaneous and were seen during phases 4 and 5. Estrous behavior of females and "love-biting" occurred in phase 6 when the stuffed toy was rubbed against the face and back of the cat. Such rubbing often caused renewed phase 1, 2, 3, or 4 activity of brief duration, after which the cat would be extremely affectionate and sensitive to being scratched on the rump.

Spontaneous vocalization occurred in some cats during and after phase 6. Apparent euphoria was sometimes seen during the entire reaction. Sleepiness or eating often occurred during or following phase 6.

A great deal of individual variation in duration and intensity of reaction was seen. Many factors, to be mentioned later, seemed responsible for this. A few cats regularly manifested phases 1 and 2, skipped phases 3 and 4, and terminated the reaction in phases 5 and 6, all within 5 minutes or less. Other cats exhibited all 6 phases with great vigor, requiring more than 15 minutes. On the average, the principal cats reacted with surprising consistency, the mean duration of response after saline solution pretreatments being approximately 10 minutes and the mean intensity of response being approximately 2.7 (Table 1).

Responses of Control Cats.—In the 1st

week, mean duration and intensity of response of the 4 control cats was 6.5 minutes and 2.5, respectively. Although response of individual cats varied from 0 to 5 minutes in duration and 0 to 1 in intensity of response in subsequent weeks, the mean values did not vary significantly ($P > 0.05$). Thus the data of the principals did not require correction for week-to-week seasonal or environmental influences on catnip reactions.

Effect of Drugs on Catnip Response.—Mean duration of response to catnip was reduced by atropine sulfate, physostigmine, neostigmine, pilocarpine, mecamlamine, methysergide, and pentobarbital (Table 1). The response was completely blocked, or nearly so, by hexamethonium, amphetamine, methysergide plus atropine sulfate, 5-HTP, and diphenylhydantoin. For more than 4 weeks after diphenylhydantoin was given, the principals still did not react normally to catnip, although the test results gradually improved during this time, as individual cats began to respond, and mean duration of response increased. Morphine, chlorpromazine, and histidine lengthened the catnip reaction, whereas atropine methyl nitrate, N-(2-chloroethyl)dibenzylamine, propranolol, and chlorpheniramine did not have a significant effect on duration of response. Mean intensity of reaction usually followed mean duration, thus analysis of the arbitrarily graded intensity data was considered unnecessary.

Specific phases of the behavioral reaction were also modified by the drugs used. Atropine sulfate prevented phase 5 grooming in 8 cats, caused 8 cats to vocalize during the reaction, and caused 4 cats to attempt to urinate. Signs of pain or fear were not seen. Atropine methyl nitrate blocked grooming in 5 cats. Physostigmine did not block grooming, but 4 cats were apparently fearful of the toy and avoided it as if repelled by it. Neostigmine produced apparent sedation; the cats did not seem to fear the stuffed toy but seemed too tired to bother with it. Pilocarpine neither in-

TABLE 1—Effect of Drugs on Duration and Intensity of Catnip-Induced Pleasure Response in Cats

Week	No. of cats	Drug given before exposure to catnip	Dose of pre-treatment drug (mg./kg. given i.p.)	Duration (min.) of response (mean \pm s.e.)	Mean intensity of response*
0	10	Saline solution	—	10.6 \pm 1.4	2.4
1	10	Atropine SO ₄	0.5	5.7 \dagger \pm 1.4	2.2
2	10	Physostigmine**	0.2	4.5 \dagger \pm 1.7	1.3
3	10	Atropine MeNO ₃	0.5	9.7 \pm 1.2	2.5
4	10	Neostigmine**	0.2	3.9 \dagger \pm 1.5	1.4
5	8	Pilocarpine**	0.15	4.5 \dagger \pm 1.6	1.8
6	8	Saline solution	—	10.4 \pm 1.3	2.8
7	8	Mecamylamine	0.7	5.2 \dagger \pm 1.4	1.9
8	8	Hexamethonium	10.0	0.8 \dagger \pm 0.6	0.5
9	8	Saline solution	—	11.4 \pm 3.3	2.5
10	8	Amphetamine	2.0	0 \dagger \pm 0	0.0
11	8	Morphine	1.0	12.6 \dagger \pm 1.1	3.1
12	8	Saline solution	—	9.0 \pm 1.2	2.6
13	8	N-(2-chloroethyl) dibenzylamine	10.0	7.3 \pm 1.6	2.4
14	9	Chlorpromazine	1.0	13.4 \dagger \pm 1.7	3.2
15	9	Saline solution	—	9.2 \pm 0.7	3.0
16	9	Propranolol	2.0	10.9 \pm 1.3	3.1
17	10	Chlorpheniramine	0.1	10.5 \pm 1.5	2.9
18	10	Saline solution	—	9.8 \pm 1.4	2.6
19	10	Methysergide	0.2	7.8 \dagger \pm 1.4	2.7
20	10	Pentobarbital	5.0	7.1 \dagger \pm 0.9	2.5
21	10	Saline solution	—	9.7 \pm 1.4	2.8
22	10	Methysergide plus atropine SO ₄	0.2 0.5	0.9 \dagger \pm 0.5	0.5
23	10	Histidine	100.0	13.5 \dagger \pm 2.3	2.9
24	10	Saline solution	—	9.6 \pm 1.2	2.8
25	9	5-Hydroxytryptophan	50.0	0.8 \pm 0.3	0.2
26	9	Diphenylhydantoin	20.0	1.6 \dagger \pm 0.6	0.6
27	9	Saline solution	—	0.7 \dagger \pm 0.5	0.4
28	9	Saline solution	—	1.7 \dagger \pm 1.0	0.4
29	9	Saline solution	—	3.2 \dagger \pm 1.3	0.9
30	9	Saline solution	—	6.9 \S \pm 1.8	1.4
31	9	Saline solution	—	7.6 \pm 1.3	2.5

* Intensity of response was scored as follows: 0 = no response; 1.0 = very weak response; 2.0 = moderate response; 3.0 = strong response; 4.0 = augmented response (stronger response than normal for the particular cat). ** Atropine methyl nitrate was also present to block muscarinic effects. † Significantly different ($P < 0.05$) from nearest normal value in saline solution experiment. ‡ Statistically nonsignificant, but still a meaningful change from control value. See text for explanation. § Two cats did not react.

duced fear reactions nor affected grooming activity.

Mecamylamine caused extreme affection in 8 cats during phase 6. Three of these cats manifested signs of sexual stimulation when stroked. Of the 3 cats, 2 were females, behaving as if in estrus. Two males placed in turn with these females did not show sexual interest. Mecamylamine also sedated the cats, which usually dozed but were easily alerted and not ataxic. Sedation was not produced by hexamethonium, and signs of increased affection were not seen, but the drug caused 5 cats to sneeze excessively during their reaction to catnip.

Amphetamine rendered the cats hyper-alert, restless, and apparently anxious. The drug did not induce signs of fear or

anger, but 2 cats developed catatonia (frozen stance while staring ahead). All of the principals ignored the stuffed toy, even though they were made aware of its presence by being rubbed with it.

Propranolol intensified phase 5 grooming activity in 4 cats, but N-(2-chloroethyl)dibenzylamine did not affect the behavior pattern.

Morphine and chlorpromazine caused increased apparent euphoria during and after the reaction to catnip. With morphine, several cats reacted with apparent urgency or frenzy, whereas with chlorpromazine the reactions seemed more deliberate.

Chlorpheniramine also induced apparent euphoria during and after the catnip reaction. The drug intensified phase 5

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grooming activity in 5 cats and rendered all of the cats more affectionate than normal during and after the reaction.

Sedation with pentobarbital, to the point of drowsiness and ataxia, but with retention of easy alerting, caused appetite stimulation before and after cats were exposed to catnip. Apparent euphoria, extreme affection, or sexual stimulation were not seen during the catnip reaction.

Methysergide induced pronounced affection in 4 cats during phase 6. Sexual stimulation was not seen, but 1 of the 4 cats had such strong apparent hallucinations that it leapt up to try and catch the phantom "butterflies" which seemed to be fluttering about the cage. Methysergide in combination with atropine sulfate caused apparent abdominal distress, nausea, emesis, and defecation before exposure to catnip. Exposure to catnip seemed to cause further such effects in a few cats, whereas others simply ignored the stuffed toy and were in no apparent discomfort.

Typical sham rage, fear, anxiety, and startle reactions were produced by 5-HTP. The pupils of the eyes were first tightly constricted, then dilated. Some cats salivated (thick tenacious saliva), panted, and had reddened ears and oral mucosa. In this condition, the cats showed little interest in the stuffed toy.

Histidine caused pronounced thin watery salivation in 4 cats during the catnip reaction. Salivation caused much head shaking in these cats, but head shaking was also seen in the cats which were not salivating profusely.

Treatment with diphenylhydantoin did not qualitatively modify behavioral phases of the catnip reaction in 5 cats which did respond to the stuffed toy. However, for more than 4 weeks after diphenylhydantoin was given, 3 cats would salivate profusely upon sight of the experimenters. During this period, 5 cats experienced temporary loss of appetite and body weight, although they were organically sound on physical examination.

Factors Affecting Catnip Response.—During pilot studies and during the main

experiment, many factors other than drug actions and side effects and individual variation were seen to modify catnip responses. These factors can be classified as environmental, physiologic, and psychologic.

New cats brought into the caged environment often did not respond to catnip for several weeks until they had gotten used to the sounds and routines of the colony. In addition, responses were immediately interrupted by strange sounds or, on one occasion, by the sight of mice in the room. Familiar sounds of food storage cans being rattled or of animal caretakers talking also interrupted the catnip reaction. Quiet conversation or the presence of a stranger in the room did not affect the response to catnip.

Physiologic phenomena, such as pain from early acute urinary obstruction, loss of sense of smell due to mild rhinitis, and copious watery salivation due to the catnip, were able to render reactors either permanently or temporarily nonreactors. Cats would also interrupt their catnip response in order to urinate or defecate. Estrus caused prolongation of the response, with pronounced apparent euphoria and affection toward the observer.

Personality and emotion were the most important psychologic factors found to affect the catnip reaction. Withdrawn, suspicious-looking cats were poor reactors or nonreactors unless in estrus or treated with a drug such as chlorpromazine, morphine, or histidine. Cats with signs of anger or fear were nonreactors unless they could be calmed. Reaction to catnip could be stopped immediately if a cat was threatened or prodded. Friendly, outgoing cats were the best reactors and were selected as replacements when necessary. A "placebo effect," or avoidance conditioning due to drug side effects or pain of injection, was seen in only 1 cat. This cat ceased reacting to catnip and became withdrawn and suspicious after the first several weeks. The cat reacted to catnip while in estrus and when treated with chlorpromazine or morphine.

Discussion

Although the ability of cats to respond to catnip has been reported heritable as an autosomal dominant,⁴¹ little attention has been given to the various factors which could cause cats to ignore catnip. Genetic determination of the catnip response must be reevaluated, since none of the cats in the present study failed to respond, given time or appropriate drug treatment beforehand.

It is assumed that neural connections exist between nasopharyngeal odor receptor cells, which are stimulated by catnip, and the olfactory lobe. It is also assumed that olfactory lobe cells connect with the hypothalamus^{32,37} and that the hypothalamus can initiate a variety of physiologic and behavioral changes after olfactory stimulation.³² The hypothalamus can activate the limbic arousal system, with subsequent effects on emotion and motivation, as well as the reticular arousal system, with subsequent effects on drive, response energy, and alertness.³³ Both arousal systems would be involved in behavioral manifestations of olfactory stimulation, and various areas of the cerebral cortex would be expected to receive facilitory or inhibitory neurons from the arousal systems in order that olfactory stimuli could be consciously sensed, integrated, and acted upon. Details of olfactory afferent paths, connections within the brain, and efferent paths have been published.^{13,32} These pathways involve synapses in many areas of the brain, and each synapse or neuron may serve as a modifier of the catnip response.

Central Cholinoceptive Components of the Catnip Response.—Existence of a *m*-cholinoceptive facilitory component of the catnip response is indicated by the fact that atropine sulfate shortened the response, but atropine methyl nitrate, which does not easily enter the brain, did not have significant effect. Ample evidence exists that there are *m*-cholinoceptive-facilitory or acetylcholine (ACH)-excitable neurons situated in the feline brain in locations suited to their possible

participation in behavioral responses to olfactory stimuli.^{7,15-17,28}

Inhibitory *m*-cholinoceptive or ACH depressible cells also exist in brain regions which may function in behavioral response to catnip.^{7,28,45} In the present study, operation of such cells was indicated when the *m*-agonist pilocarpine and the anticholinesterase physostigmine, with atropine methyl nitrate to block peripheral *m*-effects, shortened catnip reactions.

Presence of a nicotinic (*n*) cholinoceptive-adrenergic link in the central mechanisms involved in the catnip reaction was indicated when physostigmine, but not pilocarpine, caused apparent fear and avoidance of the catnip toy (sympathetic activation). Further, the *n*-antagonist mecamlamine caused signs of increased affection and sexual stimulation during and after the catnip reaction, but the *n*-antagonist hexamethonium, which does not readily enter the brain, had no such effect. Nicotinic cholinoceptive cells have been found in brain areas potentially able to function in behavioral reactions to olfactory stimuli,^{7,8,15} and there is other evidence supporting a *n*-cholinoceptive-adrenergic link mechanism in brain and behavior.^{3,23,26,35}

Central Adrenoceptive Component of the Catnip Response.—Adrenoceptive cells are found in many parts of the brain.² That some of these cells may have an inhibitory role in the catnip reaction was indicated by the fact that cats in an outwardly anxious or fearful state did not respond to catnip, but friendly cats were good reactors. When reactor cats were given the sympathomimetic amphetamine, they became restless, apparently anxious, and unresponsive to catnip. When the cats were later tranquilized with chlorpromazine, reactions to catnip were lengthened, and apparent euphoria and affection were increased during and after exposure to catnip.

Central Serotonergic Component of the Catnip Response.—Serotonin and serotonergic neurons also exist in areas of the brain which may control behavioral re-

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sponses to odor.¹² Failure of cholinomimetic and cholinolytic drugs to block the catnip response completely indicated (dose considerations aside) that some other facilitory mechanism allowed the response to proceed in the presence of these drugs.

The antiserotonin agent methysergide shortened the reaction 2 minutes, a statistically nonsignificant effect. However, 4 cats behaved as if the drug had modified phases of the response, and individual data indicated that the reaction was shortened in 6 cats.

It was believed that a mutual facilitory reciprocity between cholinergic and serotonergic mechanisms might be indicated if methysergide could abolish catnip response in the presence of atropine sulfate—neither drug being able to abolish the response by itself in the doses used. The drug combination abolished catnip response in 6 cats and drastically shortened it in 4. Analysis did not indicate a significant difference between duration of response in atropine- *vs.* methysergide-treated cats, indicating that each agent produced about the same degree of block. The difference between duration of response in methysergide- *vs.* methysergide plus atropine sulfate-treated cats was highly significant ($0.001 < P < 0.01$). These results lend support to the concept of cholinergic-serotonergic facilitory reciprocal control of the catnip response. Evidence for such pharmacologic redundancy in the central nervous system has been presented by other workers.^{18,20}

Side effects of the dose of 5-HTP used did not allow further elucidation of the role of serotonin in the behavior pattern. Prolonged ruination of the response by diphenylhydantoin prevented experiments with smaller doses of 5-HTP or with the serotonin depletor *p*-chlorophenylalanine.

Morphine has such widespread and varied effects in the nervous system that it is difficult to say exactly how the drug may have acted to prolong and intensify catnip responses. Since the cat is stimulated by morphine, it is tempting to

postulate increase of cerebral cortical ACH with *m*-facilitory cholinergic activation as the mechanism whereby responses were prolonged. Serotonin could also have been involved in facilitation of catnip responses by morphine. Part of the constipatory effect of morphine in mice was reported to be due to peripheral release of serotonin.⁹ The analgesic effect of morphine was reduced by pretreatment of rats with *p*-chlorophenylalanine,⁴⁰ and morphine tolerance and physical dependence were reduced in mice given *p*-chlorophenylalanine.⁴⁷ Thus, serotonin may mediate several central effects of morphine, including facilitation of the catnip response.

Role of Histamine in Catnip Response.—The antihistaminic drugs chlorpheniramine and propranolol did not affect duration of catnip reaction, but did intensify phase 5 grooming activity. Chlorpheniramine caused apparent euphoria and increased affection during and after the reaction, but propranolol did not. The histamine precursor histidine prolonged catnip response and caused increased affection during the response but did not alter grooming activity. Salivation was prominent and was possibly due to increased histamine levels in salivary glands. Histamine exists in the feline brain in several locations in which it could modify behavioral response to olfactory stimuli.¹ Presence of histamine indicates that it has a role in brain function, although histaminergic pathways have not yet been found. Stimulation of feline cerebral cortical neurons by application of histamine in high concentration has been demonstrated.²⁷ The same neurons were depressed by ACH and by lateral hypothalamic stimulation unless atropine was present. Antihistamines nonspecifically blocked the effects of histamine, ACH, noradrenaline, serotonin, and hypothalamic stimulation on these cortical cells, which were believed to be cholinceptive. Thus, the means by which histidine prolonged catnip response may have been by nonspecific stimulation of cholinceptive neurons.

Sedation and Catnip Response.—Seda-

tion was noticed as a side effect of mecamlamine administration and with the combination of atropine methyl nitrate and neostigmine treatment. Both treatments shortened the duration of catnip response, but the explanation for this was not apparent, since mecamlamine probably had effects in several areas of the brain, whereas atropine methyl nitrate and neostigmine were not expected to enter the brain very easily. Pentobarbital, known to almost selectively depress the reticular activating system in small doses, also shortened the duration of the catnip response. Seemingly, sedation was a partial blocker of the catnip reaction, and a normal functioning reticular-activating system was necessary for full expression of the response.

Diphenylhydantoin and Catnip Response.—Diphenylhydantoin was included in the study because it completely blocked the catnip reaction in 4 cats during pilot studies. It was used in those studies under the hypothesis that the drug, which is capable of stabilizing excitable membranes and thus rendering them resistant to changes in activity,^{42,43} should alter behavioral response to catnip if the behavior pattern relies upon altered neural function. Block of the behavior pattern by diphenylhydantoin indicates that the response does rely on unhindered function of excitable cells such as neurons. The fact that cats would not respond to catnip for several weeks after diphenylhydantoin administration, even though appetites returned to normal and there were no apparent organic abnormalities, indicates that the drug produced some type of lesion in the mechanisms which control the behavioral response.

Voluntary Component of Catnip Response.—A voluntary component of the catnip response was indicated in view of the environmental, physiologic, and psychologic factors which affected the response. Additionally, upon exposure to the catnip toy, the cats often manifested an apparent decision-making process by first scenting the toy from a distance,

then regarding the toy for several seconds, then looking away or at the observer. Finally, the cats would suddenly, but deliberately, stride up to the toy and begin sniffing and licking it. It is the volitional component of the catnip response which may have been partly blocked by sedative drugs such as pentobarbital, mecamlamine, and neostigmine.

Peripheral Components of Catnip Response.—The catnip response seemed to have peripheral as well as central components. Hexamethonium does not readily penetrate the blood-brain barrier, yet the drug abolished the catnip reaction in most of the cats. Thus, catnip response involves an *n*-facilitory mechanism which is either poorly protected by the blood-brain barrier or not within the brain at all. The latter alternative seems most probable, since another *n*-antagonist mecamlamine is not only capable of entry into the brain but caused behavioral evidence of having done so. Hexamethonium had no such behavioral effects, although hexamethonium is structurally different from mecamlamine and may not have been capable of causing the same behavioral effects as mecamlamine.

Neostigmine does not easily enter the brain, but it caused apparent sedation and shortened catnip responses. Physostigmine is known to pass the blood-brain barrier, but it did not cause sedation. Both anticholinesterases were given in the presence of atropine methyl nitrate, which blocked peripheral *m*-effects.

Phase 5 grooming activity may have had a peripheral *m*-cholinoceptive component, since this activity was blocked in several cats by the peripherally acting *m*-antagonist atropine methyl nitrate. Grooming was not blocked if neostigmine was also present. The latter drug would be expected to antagonize some of the effects of atropine methyl nitrate by allowing accumulation of ACH at *m*-cholinoceptive sites.

Proposed Interrelationships of Mechanisms in Catnip Response.—Schematic

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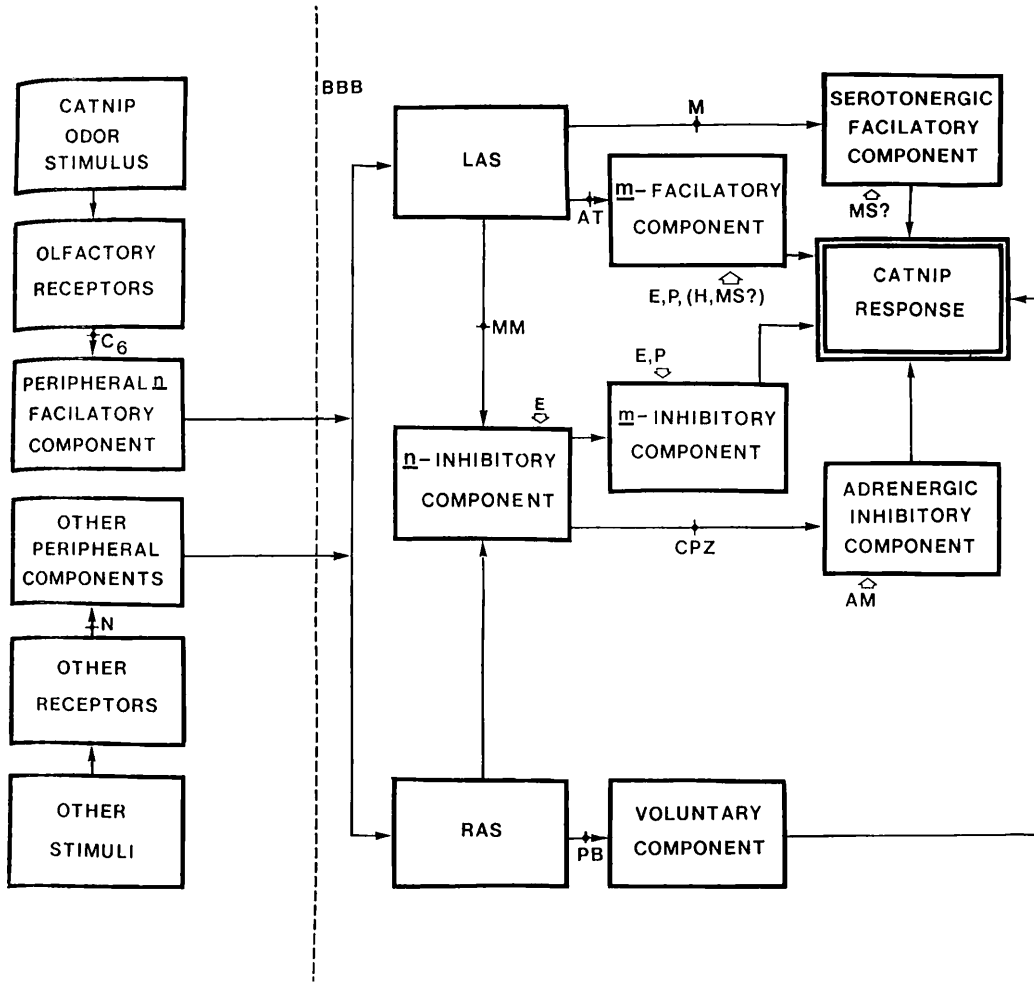


Fig. 2—Interrelationships proposed for neural control of the catnip response. Beginning at upper left, the behavior control mechanisms indicated by the experiment can be traced along routes indicated by connecting arrows. Illustrated key drugs block (●) or stimulate (hollow arrows) routes and components indicated. Abbreviations: BBB = blood-brain barrier; LAS = limbic arousal system; RAS = reticular arousal system; C₆ = hexamethonium; N = neostigmine; M = methysergide; MM = mecamlamine; AT = atropine; PB = pentobarbital; E = physostigmine (eserine); P = pilocarpine; MS = morphine; H = histidine; CPZ = chlorpromazine; AM = amphetamine; n = nicotinic cholinceptive; and m = muscarinic cholinceptive.

synthesis of brain and peripheral components of the catnip reaction as discussed in the present report is shown (Fig. 2). Actual synaptic structures or neuronal pathways should not be inferred, nor should the diagram be regarded as the only one which adequately illustrates the mechanisms involved in the complex behavior pattern studied. Furthermore, location of various facilitatory and inhibitory components in the brain cannot be assumed from cited studies in which re-

sponsive neurons were found in cerebral cortex, hypothalamus, limbic, or reticular arousal system, regardless of whether said neurons were located in or near olfactory pathways. Although behavioral response to catnip probably does rely on facilitatory and inhibitory cells in the aforementioned locations, there is evidence^{9,34} that central cholinceptive, adrenoceptive, and serotonergic components of the catnip response could exist in the olfactory lobe and that some drugs

used in the present study simply altered ability of the cats to scent catnip.

Although single doses of test drugs were used in the present study rather than graded doses, it can be seen that interrelationships proposed in Figure 2 are consistent with aspects of the 2-arousal system hypothesis of behavior,³³ with the concept of links between limbic components of behavior control³⁶ and with the idea of pharmacologic redundancy (mutual reciprocal control mechanisms) in the brain.²⁰

Conclusions

Catnip-induced pleasure behavior in cats consists of a pattern of actions which is quantifiable in terms of duration and intensity. The fact that the behavior pattern is predictable and easily reproduced indicates a degree of automaticity or stereotypy in its mediation. However, the fact that the reaction was modified by several centrally and peripherally acting drugs of known action, by several environmental, physiologic, and psychologic factors, and by an apparent volitional element attests to the complexity and high degree of organization of the overall behavior pattern.

Use of numerical data of drug effects on duration of response, objective and subjective assessment of behavioral effects of drugs and other factors on the response, and knowledge of the pharmacologic nature of cell types in brain regions associated with olfaction and arousal allowed synthesis of a possible scheme of control interrelations for the catnip response. The fact that these postulated control mechanisms support current hypotheses of behavior control, and that the behavior control hypotheses support the postulated mechanisms of control of the catnip response, indicates that the catnip response may be useful in the study of pleasure behavior and olfaction. In addition, the similarity of aspects of the catnip response to the effects of marijuana and LSD in man, the structural similarity of nepetalactone to portions of the LSD and tetrahydrocannabinol molecules,

and the fact that catnip is psychedelic in man indicate that catnip-induced pleasure behavior in cats may be useful as an animal model for the study of mind-altering drugs and their antidotes in man.

Further investigation of the catnip reaction seems warranted.

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