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Anorexia and Hyperphagia Produced by Five Pharmacologic Classes of Hallucinogens

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VAUPEL, D. B. AND E. C. MORTON. *Anorexia and hyperphagia produced by five pharmacologic classes of hallucinogens*. PHARMAC. BIOCHEM. BEHAV. 17(3) 539–545, 1982.—The acute actions of five prototype hallucinogens administered SC on food consumption in 23 hr food deprived dogs were compared with the anorexic effect of *d*-amphetamine and the hyperphagic effect of sodium pentobarbital. Comparisons were made on the basis of dose-response relationships. Among the hallucinogens decreasing food intake, both LSD and atropine produced substantial anorexia, but the slopes of their dose-response curves were clearly different from *d*-amphetamine. Phencyclidine and the opioid SKF 10,047 suppressed food intake also; their individual dose-effect curves were parallel to the amphetamine curve, although both were less potent. Of the hallucinogens tested, only delta-9-tetrahydrocannabinol (Δ^9-THC) stimulated food consumption, and though it was less potent, it resembled pentobarbital both qualitatively and by having a parallel dose-response curve. The appetitive responses are discussed in relation to other pharmacologic actions of these hallucinogens in the dog, and consideration is given to the possible modes of action for phencyclidine- and SKF 10,047-induced anorexia.

Food intake studies Hallucinogens LSD Atropine Phencyclidine SKF 10,047
Delta-9-tetrahydrocannabinol Amphetamine Pentobarbital Anorexia Hyperphagia

AN approach for evaluating the abuse liability of drugs has been to use the degree of pharmacologic equivalence which exists between drug prototypes, whose animal and clinical pharmacology is established, and test drugs. As developed in humans this is a broad approach using physiologic, subjective and behavioral measures and has successfully been employed with opiates, sympathomimetic amines, barbiturates and hallucinogens at the Addiction Research Center for over 25 years. With increasing restrictions on human research, this methodology has been adapted to the dog by incorporating objective physiologic measures and the subjective rating of canine behavior to provide a mixture of both analogue (isomorphic) and assay (parallel) animal pharmacologic models [20,44]. The experimental paradigms used to determine pharmacologic profiles include single dose effects, tolerance and cross tolerance to LSD, substitution and precipitation studies in opiate dependent animals and antagonism studies.

Extensive studies with both opiates [11, 28, 31, 32] and LSD-type hallucinogens [33,45] in the chronic spinal dog have shown that this species provides a valid animal model with which to assess the abuse liability of these drugs. Food intake was not measured systematically in opiate studies. However, in a study of ring-substituted amphetamine compounds with LSD-like properties acute drug effects on appetitive behavior were incorporated because anorexia is an important action of *d*-amphetamine in man. Food intake can be readily quantitated and it can function as an analogue and assay model in the dog. The results demonstrated that the depressant effects of LSD on food intake could be distinguished from *d*-amphetamine based on the shallower slope of the LSD dose-response curve [47]. Yet four methoxylated amphetamine derivatives retained an amphetamine-like ability to decrease food intake based on dose-response characteristics, although they are pharmacologically equivalent to LSD based on profiles from single dose, cross tolerance and antagonism studies.

An outgrowth of the substituted amphetamine study was to develop characteristic single dose profiles for different prototype hallucinogens and to include acute drug effects on food intake as one behavioral measure. This paper presents the results of that part of this effort. Drug prototypes and their classifications were as follows: (1) atropine-belladonna alkaloids (deliriants); (2) lysergic acid diethylamide (psychedelics of the LSD class); (3) phencyclidine (arylcyclohexylamines: dissociative anesthetics); (4) SKF 10,047 (opioid agonist-antagonists) and (5) Δ^9-tetrahydrocannabinol (cannabinoids). Being representatives of different classes of drugs the prototypes are diverse both in structure and actions. However, these classes share a common link in that they are abused hallucinogens and present public health and social problems. Specific interests included a comparison of the appetitive effects of phencyclidine and SKF 10,047, since it was initially shown in the spinal dog that these compounds produce almost identical single dose effects [21,46] and that they share similar discriminative stimulus properties in the rat [21,41]. Further, their profiles in the dog include several amphetamine-like actions (marked mydriasis, retraction of the nictitating membrane, hyperthermia and stereotyped head movements). Atropine and Δ^9-tetrahydrocannabinol (Δ^9-THC) were included since their single dose profiles had already been established. The comparison of atropine and

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phencyclidine was of interest since an anticholinergic mode of action has been hypothesized for phencyclidine [26].

Among the hallucinogens tested only Δ^9-THC stimulated food consumption; all other compounds depressed it. For those compounds exhibiting appetite suppressant effects, atropine and LSD could be differentiated from *d*-amphetamine by the slopes of their dose-response curves. Such a differentiation could not be made between phencyclidine, SKF 10,047 and amphetamine.

METHOD

Subjects

Beagle-type dogs of either sex weighing between 8.5 and 16.7 kg and having an estimated age range of 2 to 7 yr were selected for the experiments. Dogs were housed in individual cages in a large colony room whose lights were on between 0600 and 1800 hr. Water was available ad lib. Altogether 16 different dogs (3 M and 13 F) were employed, but only 12 dogs participated at any one time. After testing LSD, the first drug to be investigated, 4 of the original 12 dogs were replaced, and with this exception the same 12 dogs received all treatment conditions.

Food Intake

Following the procedure of Nozaki *et al.* [37] 500 g of food (Purina Dog Chow) was made available to each dog for a 1 hr period every morning in the home cage, and the amount of food ingested was recorded to the nearest gram and corrected for spillage. Control levels of food intake stated as grams/dog/day were determined by averaging the amount ingested over the 5 days preceding the test day and the 5 days following the day after test day. On the day prior to testing, dogs were weighed to determine injection volumes. Test sessions were conducted once a week with the drugs being injected SC 1 hr prior to feeding. Periodic behavioral observations were made during the feeding period on test days. The quantity of food consumed on the test day was expressed as a percentage of the average control value.

Experimental Design

Multiple doses of either one or two drugs and a vehicle were administered using six randomized or partially randomized block designs (Dogs × Treatments). The experimental block sequence was as follows: (1) LSD and saline; (2) phencyclidine and saline; (3) sodium pentobarbital; (4) atropine, *d*-amphetamine and saline; (5) Δ^9-THC and vehicle; and (6) SKF 10,047 and vehicle. In most instances the doses were geometrically incremented by a factor of either 2 or 4. Dose-ranging studies were typically conducted before starting a new block of experiments. An additional dose was sometimes added after completing a block. Twelve dogs were incorporated into each block and drug treatments were completely crossed over.

Drugs

Drug solutions were prepared on the morning of the test day. Concentrations were formulated to deliver the unit dose (mg/kg) in a volume of 0.2 cc/kg. Dosages were based on the following salt or free base forms: *d*-amphetamine sulfate, atropine sulfate, lysergic acid diethylamide tartrate, sodium pentobarbital, phencyclidine hydrochloride, SKF 10,047 free base and Δ^9-THC. Δ^9-THC (166 mg/ml dissolved in 70 percent ethanol) obtained from the Arthur D. Little Company (Lot number THC ADL 16972-78 with a specified purity of 98 percent) was diluted in 70 percent ethanol (v/v) to appropriate concentrations. SKF 10,047 was dissolved in a 3:2 ratio of 8.5 percent lactic acid and 1 N NaOH. Saline was the vehicle for all remaining drugs.

Data Analysis

Analyses of variance were used to identify the between-subjects and the within-treatment components for each drug. To evaluate dose-response relationships, the treatment variance was either partitioned into linear regression and deviations from linearity terms or orthogonally partitioned for polynomial curve fitting whenever doses were geometrically spaced. Separate regression analyses were used to determine the best-fit equations. Relative potencies were determined using standard parallel line bioassays for crossover data [9]. The effectiveness of single doses in altering food intake as compared with vehicle effects was assessed using two-tailed paired *t*-tests. The criterion for statistical significance was considered to be $p<0.05$.

RESULTS

Baseline Food Intake Values

Over the course of the study the average food intake was 231 g/dog/day with a range of 161 to 377 g for all 16 dogs. To assess the stability of baseline food intake levels, 12 week control intake averages were obtained for the beginning (months 1–3), middle (months 10–12) and end (months 21–23) of the study. During the final period, dogs were consuming less food. This was best observed in the eight dogs completing the entire study as their 222 g end baseline intake level was less than the beginning (252 g; $p<0.05$) and middle (250 g; $p<0.01$) average intake values.

Vehicle Effects

Saline was administered on three occasions with no difference found between the group means (101±9 percent, 87±7 percent and 107±8 percent). Figure 1 shows the pooled results of these three trials and the confidence limits. Among the effects of the two other vehicles, neither the SKF 10,047 lactic acid-sodium hydroxide vehicle (110±7 percent) nor the Δ^9-THC ethanol vehicle (84±11 percent) differed from saline. The ethanol vehicle did produce skin ulcerations in some dogs.

d-*Amphetamine*

d-Amphetamine decreased the quantity of food ingested in a dose-dependent, linear, $F(1,33)=67.58$, $p<0.01$, manner. The effects of the three highest doses, 0.035, 0.07 and 0.21 mg/kg, were significantly different from saline control values (Fig. 1). Importantly, none of the doses of *d*-amphetamine overtly increased locomotor activity or produced stereotyped behavior.

Atropine

Atropine effectively decreased food intake, but its dose-response curve was not parallel to *d*-amphetamine as determined by a 9 point bioassay. Analysis of the atropine data revealed significant linear, $F(1,44)=54.89$, $p<0.01$, and quadratic, $F(1,44)=9.64$, $p<0.01$, components. Consequently

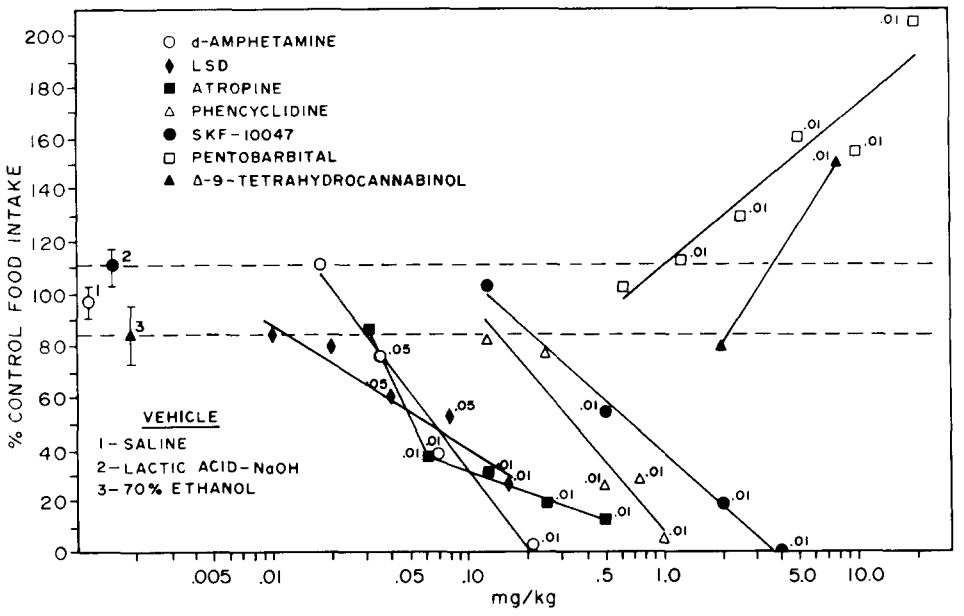

FIG. 1. The acute effects of hallucinogens representing different pharmacologic classes on food intake in 23 hr food deprived dogs. The saline control response is the mean of three replicates averaged together in each of 12 dogs, and the 95 percent confidence limits are indicated by the dashed lines. Standard errors are shown only for the vehicle controls. Δ^9-THC was dissolved in 70 percent ethanol, and SKF 10,047 in a lactic acid-sodium hydroxide vehicle. Saline was the vehicle for all other drugs. Vehicle-drug comparisons are based on paired t-tests with the level of significance ($p<0.05$ or $p<0.01$) shown by the superscript. For saline-drug statistical comparisons, only the individual saline control corresponding to the appropriate block of experiments was employed. Dose-effect relationships are indicated by calculated regression lines. The n is 12 for all data points. Dosages are based on the forms stated in the methods section.

the curve was subdividied into two linear segments with an inflection point at the 0.0625 mg/kg dose (Fig. 1). Not illustrated is a 117 percent response of three dogs receiving 0.0156 mg/kg of atropine obtained in a dose-ranging experiment. This data point is consistent with the division of the data as illustrated in Fig. 1. The upper portion of the atropine curve had the steepest slope and a bioassay analysis demonstrated that atropine was equally potent to amphetamine over a restricted dose range (Table 1). That portion of the atropine curve produced by 0.0625 mg/kg and the three higher doses had a much shallower slope and did not parallel the amphetamine curve. The result was a distinct nonlinear curve for decreasing food intake. Another notable effect of atropine was pronounced mydriasis observed with the two highest doses. Thus with relatively low dose levels, atropine was capable of decreasing food intake in the absence of other observable physiological or behavioral effects but the appearance of mydriasis suggests that other unmeasured actions may be manifesting themselves with high doses which could in part affect the responses of the dogs.

Lysergic Acid Diethylamide

LSD was effective in linearly, $F(1,44)=29.15$, $p<0.01$, diminishing food intake but the slope of its regression line was significantly less than that of *d*-amphetamine. This was evidenced by nonoverlapping 95 percent confidence limits of their slopes and by an invalid bioassay analysis (Table 1). In addition to eating less, dogs receiving the high LSD dose (0.16 mg/kg) exhibited increased locomotor activity and vocalizing, which consisted predominantly of barking interspersed with episodes of whining and howling. For this reason higher doses were not evaluated. It was concluded that the effects of LSD and *d*-amphetamine on food intake could be characterized by linear dose-effect curves with differing slopes, and that LSD lacked the specificity of amphetamine as the appearance of additional and potentially disruptive behavioral effects coincided with the most efficacious dose of LSD.

Phencyclidine

Phencyclidine reduced food intake in doses greater than 0.25 mg/kg (Fig. 1) and the data for the five doses (Table 1) demonstrated significant linear, $F(1,33)=71.61$, $p<0.01$, and cubic, $F(1,33)=5.36$, $p<0.01$, components. A valid 8 point bioassay was obtained comparing *d*-amphetamine with phencyclidine (Table 1) and estimated phencyclidine to be one-fifth as potent as *d*-amphetamine. Other effects including stereotyped head movements, staring and copious salivation accompanied the appetite reduction produced by the 1.0 mg/kg dose of phencyclidine. Although less potent as an anorectic, phencyclidine resembled *d*-ampehtamine in its capacity to almost totally suppress food intake. However, unlike amphetamine, at a maximally suppressant dose of phencyclidine the emergence of additional pharmacologic effects in a majority of dogs was readily apparent.

TABLE 1

BIOASSAY EVALUATIONS OF THE ANOREXIC AND HYPERPHAGIC EFFECTS OF HALLUCINOGENS ON FOOD INTAKE IN 23 HR FOOD DEPRIVED DOGS

Drugs Decreasing Food Intake		Drugs Increasing Food Intake	
d-Amphetamine	1.00	Pentobarbital	1.00
Atropine	1.01 (0.73–1.40)*	Δ^9-Tetrahydrocannabinol	0.40 (0.22–0.60)¶
LSD	Invalid bioassay†		
Phencyclidine	0.17 (0.098–0.25)‡		
SKF 10,047	0.082 (0.038–0.14)§		

The numerical values represent relative potency estimates with their 95 percent confidence limits shown in parentheses. The relative potencies of the two standard drugs, *d*-amphetamine and pentobarbital, were set equal to 1.00. Relative potency is defined as the mg of the standard drug equal to 1.00 mg of the investigational drug.

*Potency estimate applies only to the upper segment of the nonlinear atropine dose-response curve. A 4 point bioassay: 0.0312 and 0.0625 mg/kg of atropine and 0.035 and 0.07 mg/kg of *d*-amphetamine.

†The dose-response curves for LSD and *d*-amphetamine were not parallel. An 8 point bioassay: 0.01, 0.02, 0.04, 0.08, and 0.16 mg/kg of LSD and 0.035, 0.07 and 0.21 mg/kg of *d*-amphetamine.

‡An 8 point bioassay: 0.125, 0.25, 0.5, 0.75 and 1.0 mg/kg of phencyclidine and 0.035, 0.07 and 0.21 mg/kg of *d*-amphetamine.

§A 7 point bioassay: 0.125, 0.5, 2.0 and 4.0 mg/kg of SKF 10,047 and 0.035, 0.07 and 0.21 mg/kg of *d*-amphetamine.

¶The 5 point bioassay (1.25, 2.5 and 5.0 mg/kg of pentobarbital and 2.0 and 8.0 mg/kg of Δ^9-THC) demonstrated a significant difference between preparations, consequently the confidence limits have a limited utility.

SKF 10,047

The anorexigenic property of SKF 10,047 was demonstrated to be linear, $F(1,33)=114.18$, $p<0.01$, over a dose range of 0.125 to 4.0 mg/kg (Fig. 1) and a valid bioassay with *d*-amphetamine with SKF 10,047 was obtained (Table 1). Stereotyped head movements were noted in 3 of the 12 dogs receiving the high dose (4.0 mg/kg). These data demonstrated that SKF 10,047 and *d*-amphetamine were equally efficacious in suppressing food consumption and had parallel dose-response curves. On a mg/kg basis SKF 10,047 was approximately one-tenth as potent as *d*-amphetamine and produced relatively few behavioral effects at a dose that completely abolished food intake.

Pentobarbital

Pentobarbital in doses of 0.625 mg/kg to a markedly ataxic dose of 20 mg/kg linearly, $F(1,55)=53.71$, $p<0.01$, increased the quantity of food ingested (Fig. 1). With higher doses it was sometimes necessary to provide more dog chow during the test period when it became apparent that the 500 g allotment would be completely consumed. Thus, the stimulant effect of pentobarbital on canine ingestive behavior was clearly the opposite of amphetamine and permitted an examination of the relationship between pentobarbital and Δ^9-THC, the only hallucinogen found to reliably increase appetite in the dog.

Delta-9-Tetrahydrocannabinol

Consummatory behavior was significantly increased by 66 percent over the vehicle response by 8 mg/kg of Δ^9-THC (Fig. 1). The effects of lower doses of Δ^9-THC, 0.125, 0.5 and 2.0 mg/kg, were respectively 100 percent, 96 percent and 79 percent, did not differ from control values and exhibited no regression. The 2.0 and 8.0 mg/kg data had a highly significant linear regression, $F(1,11)=37.65$, $p<0.01$, (Fig. 1) and Δ^9-THC was about half as potent as pentobarbital in producing hyperphagia (Table 1). Following the 8.0 mg/kg dose, the behavior of the dogs appeared unaffected during the test session. However, at feeding time the following day most of the dogs were atypically lethargic and remained at the back of their cages. Normally the dogs would have immediately come to the front of their cages when the food pans were presented. Thus, the relatively rapid stimulation of appetitive behavior by Δ^9-THC was followed by a delayed behavioral deficit manifested as lethargy. Within the entire series of experiments, Δ^9-THC was the only one of five prototype hallucinogens tested to increase food intake in the dog.

DISCUSSION

Amphetamine anorexia and pentobarbital hyperphagia are reliably produced in the dog as shown in this study and others [1, 2, 5, 22]; however, in man only the anorexic effect of amphetamine has been reproducible. Effective doses of amphetamine in the dog were comparable to those in man in which 0.1 to 0.4 mg/kg SC decreased caloric intake [30]. In a classic study of barbiturate intoxication, Isbell *et al.* [19] reported that patients decreased their caloric intake while gaining weight. In a subsequent barbiturate study, not specifically designed to assess appetite, some subjects appreciably gained weight and made frequent trips to the kitchen for snacks as compared to control periods and studies with opiates (H. F. Fraser, personal communication). Overall, data showing that barbiturates enhance appetite in man is not consistent and similar findings have been reported for subhuman primates [14,49]. In contrast the barbiturates have been shown to increase food consumption or food rewarded behavior in mice and rats [3, 39, 43]. Therefore barbiturate hyperphagia may be species dependent. The production of

amphetamine anorexia without other grossly observable pharmacologic changes is consistent with the utility of the dog as an analogue model of appetite suppression, but the evidence is not as compelling for pentobarbital hyperphagia.

With respect to mechanisms of action the interpretation of dose-response curves in this study must be considered suggestive and not conclusive evidence due to the global nature of the eating behavior measured. Of primary interest were the parallel dose-response curves of SKF 10,047, phencyclidine and *d*-amphetamine. This suggests similar modes of action and agrees with data describing amphetamine-like effects for the former two drugs as presented in the Introduction. Phencyclidine interacts with several putative neurotransmitter systems, one of which is the presynaptic release and re-uptake blockade of dopamine [7, 8, 10, 36] and thus could possibly mimic amphetamine [4,25] in this manner. Aside from the qualitative notation of SKF-induced anorexia [34] and this report, nothing is known about how SKF 10,047 affects appetite. The effect could be nonspecific [17] or result from an interaction with dopaminergic or endorphin [12, 16, 23, 27] systems. The latter is of interest in view of the numerous reports [12, 13, 27, 40] which followed Holtzman's [16] description of the appetite suppressant property of the opiate antagonist naloxone. It is also notable that as maximally effective anorexic doses of amphetamine were approached other observable effects were not seen, whereas a majority of dogs receiving phencyclidine and a few with SKF 10,047 showed additional drug effects indicating lower specificities of action.

The depressant actions of LSD and atropine on food intake can best be utilized as part of their overall pharmacologic profiles. In the chronic spinal dog a 15 μg/kg dose of LSD elicits a reproducible and characteristic profile [33,45]. The most effective dose employed in this study was some ten times larger (although SC), produced a 70 percent reduction in food intake and caused appreciable behavioral effects which most likely contributed to a nonspecific disruption of feeding behavior. Among the hallucinogens tested, LSD was the least efficacious and was readily identified by its shallow dose-response curve. Atropine reduced food intake with mydriasis developing at the two highest doses (0.25 and 0.5 mg/kg). For comparison mydriasis and tachycardia were observed with 0.1 and 0.2 mg/kg of atropine IV administered to the chronic spinal dog, while additional behavioral changes such as restlessness, whining and howling developed with 0.3 and 0.4 mg/kg IV (Vaupel, unpublished observations). Within this study the two phasic effect of atropine on food intake contributed a distinctive action to its overall profile in the dog. The dose-response curves of atropine and phencyclidine also had differing geometries suggesting that phencyclidine may not share the same mode of action as the anticholinergic blocker atropine in altering food intake.

The historical reputation of marihuana for stimulating appetite [48] has been verified clinically [13,15]. A review of animal studies [42] indicated that Δ^9-THC is primarily an anorexigen in rats but stimulates food intake in sheep [29] and dogs [18]. Our finding that Δ^9-THC enhances food intake in dogs is consistent with its acute action in man. Besides its hyperphagic effect, Δ^9-THC in adequate doses produces a unique syndrome in the dog characterized by static ataxia [6,48] and an enhanced startle response [6]. Together these three actions raise the prospect of utilizing the dog as a species for evaluating cannabinoid derivatives that may enhance appetite while lacking the capacity to produce sedation. Such compounds could have potential utility as treatment modalities for appetitive disease states such as anorexia nervosa or loss of appetite associated with cachexia.

A cautious interpretation of the present results should be considered due to the nonspecific nature of food intake; factors not solely related to the motivation of hunger may contribute to the reported changes. These factors could include peripheral signals, conditioned taste aversion, alterations in locomotor activity, changes in sensory or sensorymotor function and cognition [24,38]. Reference has already been made to specific drug effects observed concomitantly with food intake changes. Data in man also suggest that general sensory effects of drugs appear to precede physiologic effects and acute signs of intoxication [24,35]. Thus, knowing that the drugs evaluated in this study are capable of altering sensory perception in man, it seems tenable that the food intake responses of dogs may be dependent to a degree on similar influences.

In summary, the effects of five hallucinogens on food intake in the dog were characterized by their dose-response curves. None was more potent or as selective in producing anorexia than *d*-ampehtamine, which clinically produces hallucinogenic phenomena in the form of a paranoid toxic psychosis. LSD and atropine produced anorexia and their dose-response curves were distinctly different from *d*-amphetamine. Parallel dose-response curves for food intake suppression were produced by *d*-amphetamine, phencyclidine and SKF 10,047. However, differences in selectivity were observed; at doses producing almost complete anorexia additional behavioral effects were observed for phencyclidine and to a lesser extent for SKF 10,047, but not for *d*-amphetamine. On the other hand Δ^9-THC, although less potent, resembled pentobarbital by enhancing food intake in a parallel manner. Together, the appetitive behavioral responses as determined by changes in food intake provide pharmacologic information that complements data in the chronic spinal dog in developing whole animal pharmacologic profiles for prototype hallucinogens.

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