GINSENG SELF-ADMINISTRATION IN MONKEYS

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Abstract

Four monkeys (*Macaca mulatta)* were allowed to press a lever in their cages in order to earn access to one gram pieces of *Panax ginseng* root. Self-administration performance on an operant schedule (mult FR20 F11) was characterized by frequent pauses and increased intertrial interval responding. When given 23 hour unlimited access to ginseng root, as well as to food and water, all animals titrated their daily intake to approximately 1.5 g/kg. Gross behavioral changes included increases in vocalization, activity, stereotyped movements, and weight loss. These patterns of behavior are typical of those seen when monkeys self-administer psychomotor stimulants. Further studies on ginseng's reward value can be conducted using this animal model.

Introduction

It has been a traditional finding of experimental psychopharmacology that animals will self-administer those same drugs that are abused by man (Griffiths, Bigelow, & Henningfield, 1980). The general method provides animals with access to a manipulandum, such as a lever, and responding on the manipulandum results in delivery of the drug. The model has been established using a variety of species (e.g., rat, dog, cat, monkey, baboon), types of responses (e.g., lever press, panel press), and routes of drug administration (e.g., intravenous, oral, intragastric, inhalation). The model is useful in that it can predict substances that may be rewarding to humans and subsequently subject to possible abuse. Drugs abused by man and self-administered by animals include narcotics, psychomotor stimulants, central nervous system depressants, anti-histamines, and even some hallucinogens. Conversely, drugs rarely abused by man are not self-administered by animals and these include major tranquilizers, antidepressants, and nonnarcotic analgesics.

In addition, establishing drug self-administration behavior under controlled conditions in the laboratory provide an opportunity to gain valuable information about human use of the same substance. The well-known clinical uses of ginseng preparations coupled with recent reports of adverse reactions (Lu, 1976) and abuse resulting from large chronic dosages (Siegel, 1979) suggest the need for an animal model in order to understand the reinforcing properties of this substance. Therefore, the present study was designed to investigate the self-administration of ginseng by animals.

Method

Subjects

Four male rhesus monkeys (*Macaca mulatta*), approximately 4 years old and 12 kg, were used as subjects. The monkeys had been used previously in behavioral studies with hallucinogens and cocaine. However, they were drug-free for 6 months at the start of the present experiment.

Topography of Ginseng Chewing in Monkeys

In preliminary studies with other monkeys in the laboratory, it was observed that monkeys would readily accept pieces of ginseng root, moisten them with saliva, and push them into their cheek pouches for sucking and rechewing. After several minutes of chewing, the monkeys would swallow the entire amount of ginseng. Variations in the size, shape, and texture of ginseng roots would often induce the monkeys to spend considerable periods of time inspecting the ginseng, sometimes breaking the roots apart and discarding uneaten portions. In an effort to eliminate these behaviors and allow for the use of a uniform preparation, standardized ginseng pellets were prepared according to the following procedure.

Preparation of Ginseng and Placebo Pellets

Ginseng pellets were prepared from commercial white ginseng roots (*Panax ginseng*). These roots contained between 0.5% and 3.0% panaxosides (Liberti & Marderosian, 1978). Roots were coarsely ground and compressed into spherical pellets containing 1.0 g ginseng root powder, gum arabic, and banana flavoring. For preparation of placebo pellets, steamed bone meal powder was mixed with collagen protein, water, hydrogenated vegetable oil, calcium chloride, sucrose, vitamin-mineral supplements, and yellow food coloring. This powder was compressed into spherical pellets containing 1.0 g mixed powder, gum arabic, and banana flavoring. Human observers judged that the resulting placebo pellets resembled the white ginseng pellets in texture, color (pale yellow), and aroma. However, the ginseng pellets were judged to have a slightly sweeter taste than the placebo pellets. Analysis of the placebo pellets indicated 15.8% protein, 9.0% moisture, 4.8% fat, 3.0% fiber, 60.9% carbohydrates, and 300 calories/100g. This analysis compares favorably with the nutritional analysis of ginseng root itself (Warf Institute Report No. 7031080 for the USDA Plant Taxonomy Laboratory, March 1977). Both ginseng and placebo pellets were readily accepted and ingested by monkeys.

General Procedure

Four rhesus monkeys were individually trained in operant units (lm × lm × lm) equipped with 2 levers (right and left side of front panel), cue lights located over each lever, and a reinforcement delivery chute below each lever. The chutes were connected to separate universal feeders (Ralph Gerbrands Company, Model 120) and all programming was controlled by conventional electromechanical and solid-state equipment. Behavior could be monitored by a closed-circuit television camera with microphone. A single 25 watt house light illuminated the unit.

The animals were trained according to the following general procedure. During a 5 minute intertrial interval (ITI), a single white light located over the center of a lever was illuminated and responses had no programmed consequences. A trial began when the white light and a side colored light were illuminated. A red side light was paired with placebo pellets, a green light with ginseng pellets, and a blue light with food pellets (Purina monkey chow pellets). Completion of 10 responses or a fixed ratio 10 (FR10) delivered 1 pellet to the chute signaled by a brief white light located over the chute. Additional lever responses at this point had no programmed consequences. When a photocell circuit indicated that the monkey had removed the pellet from the chute, the ITI began. When a single lever was available in a session, lights over the other lever were dark. The availability of the right or left lever was randomly alternated between sessions. When both levers were available within a session (choice tests discussed below), lights over both were il-

luminated and extinguished at the same times. In such 2 lever sessions, responses on one lever did not accumulate on the other and independent FR10 schedules were required. Once a reward was delivered, responses on the other lever had no programmed consequences. Responding on both levers remained ineffective until the end of the ITI when cue lights were again illuminated and new FR10 schedules were required with no savings of previous responses.

Initially, the monkeys were deprived of their normal diet of Purina monkey chow pellets for 21 hours and trained to respond for food pellets. At the end of each daily session, animals were supplemented in their home cages with food pellets and fresh fruit. Water was freely available in operant units and home cages. After several training with food pellets, all four monkeys were earning most of their daily food within a maximum 4 hour session, and performance stabilized with less than a 10% daily change in responses. At that point, the animals were gradually shaped to respond on a multiple fixed ratio 20, fixed interval 1 minute schedule with a limited hold of 1 minute. (mult FR20 FI1). This schedule required the animal to make 20 lever responses (FR20) in order to be rewarded with delivery of a food pellet. Subsequently, the fixed interval component determined that the first response occurring after an interval of 1 minute (FI1) was reinforced with food pellet delivery. The limited hold set up a short period (1 minute) during which a reinforcement arranged by the interval schedule was held available. At the end of a limited hold, a response would not be reinforced until another reinforcement had been set up. In addition, there was a time out for 5 minutes following each reward in order to enable the animal adequate time to consume the pellets. During this time out, all key lights were dark and responses had no programmed consequences. The mult FR20 FI1 schedule was chosen because of its unique sensitivity to changes induced by psychomotor stimulants. Thus, the schedule could allow for both the self-administration of ginseng and the detection of any psychomotor stimulation it may produce.

Over the next 5 transitional sessions, placebo pellets were gradually substituted for food pellets while food pellets became freely available in a separate food container located within the operant unit. Concomitantly, the sessions were gradually lengthened until the animals were spending 23 hours per day in the unit with placebo pellets always available on the mult FR20 FI1 schedule and food and water independently available *ad libitum*. The animals were removed from the units for 1 hour each day so as to allow for cleaning of the unit, removal and weighing of discarded pellets, removal of urine samples collected automatically in the unit, and weighing of the animals.

Results

Self-Administration Behavior

During a subsequent block of 10 consecutive sessions, only placebo pellets were available. This was followed by another block of 10 consecutive sessions wherein only ginseng pellets were available. Table 1 summarizes these sessions in terms of the total number of pellets earned by each monkey in each session. Here it can be seen that during placebo sessions, monkeys were earning an average of 2.0 pellets per session. Of these, approximately 1 pellet per session was discarded in an uneaten or partially chewed condition. Conversely, during ginseng pellet sessions, monkeys were earning an average of 15.1 pellets per session. Of these, approximately 4.8 pellets per day were discarded by each animal.

There were apparent differences in responding during placebo and ginseng sessions. During placebo sessions, animals responded very little, averaging only 100 to 400 responses per session. Most of these responses were given during the fixed ratio component and little or no responding occurred during the fixed interval, time out, or ITI periods. Conversely, during ginseng sessions, animals averaged over 1300 responses per session. All animals showed some disruption of stimulus

Table 1. Total pellets earned by each monkey in each session

	monkeys			
	C1	C2	C3	C4
Placebo Sessions				
1	5	4	2	2
2	4	3	0	1
3	2	2	0	4
4	1	2	0	0
5	2	1	0	2
6	3	2	1	5
7	1	3	2	2
8	1	6	4	3
9	0	4	1	0
10	2	6	0	0
Total	21	33	10	19
	C1	C2	C3	C4
Ginseng Sessions				
1	21	13	9	16
2	2	38	8	12
3	5	31	13	14
4	16	25	21	15
5	8	20	6	19
6	12	29	4	18
7	19	11	1	6
8	20	35	14	14
9	0	18	4	19
10	15	23	5	26
Total	118	243	85	159

control as mean ITI responding increased from placebo rates of 0.10 responses per minute to 0.35 responses per minute during ginseng sessions. Concomitantly, FR responding, particularly near the end of the sessions. was interrupted with frequent pauses. Responding also increased slightly during the initial part of the fixed interval.

Gross behavioral changes were also evident during ginseng sessions. Most animals readily accepted and ate the first 5 ginseng pellets within the early part of each session. This was usually followed by periods of pacing around the operant unit, increased visual orienting responses, and increases in general activity. One monkey, C2, repeatedly displayed startle reactions and all monkeys manifested considerable facial grimacing. There was a significant increase in stereotypic movements including teeth grinding, lip-smacking, and rocking—behavior associated with states of psychomotor excitation. After a pause of 5 to 7 hours, monkeys would once again respond for ginseng pellets. This pattern of spaced self-administration is similar to the pattern seen when monkeys are responding for stimulants such as cocaine or amphetamine.

Titration Behavior

An additional 20 sessions with ginseng pellets were given to all monkeys. During these sessions, performance remained stabilized at an average of 15 pellets earned and 5 pellets discarded per session. Monkeys sometimes ignored for serveral hours their food and fruit which were freely available at all times in the operation unit and weight losses, albeit insignificant, were recorded for most animals. In addition, the animals appeared continually hyperactive throughout these ginseng sessions.

Choice Tests

A series of choice tests were conducted in order to determine pellet preferences. In any given choice session, 2 types of pellets (ginseng and placebo) were available, one type on each lever. Appropriate colored lights signaled the identity of the pellet available and the lever on which any given pellet was available was randomly alternated between sessions. Four consecutive sessions were run on a choice situation between ginseng pellets and placebo pellets. Sessions were run until a total of 15 pellets were delivered or 23 hours elapsed, whichever event occurred first. The results of these tests are presented in Table 2 in terms of the total number of pellets earned and discarded by each monkey. The maximum number of pellets available over the 4 separate choice sessions was 60. It is clear from this data that all monkeys preferred ginseng pellets over placebo pellets. Most of the discarded pellets had been

Table 2. Total number of pellets earned and discarded (in parentheses) by each monkey in four choice sessions.

Monkeys	Placebo pellets	vs.	Ginseng pellets
C1	4 (1)		43 (21)
C2	6 (6)		51 (10)
C3	1 (0)		22 (8)
C4	3 (1)		36 (24)

partially chewed. This suggests that animals may have discriminated between pellets on the basis of subtle taste cues.

Discussion

The most apparent aspect of these findings is that monkeys will self-administer ginseng via oral ingestion when given an experimental opportunity to do so. By pressing a lever according to a complex schedule of responses, monkeys consistently worked for the reward of ginseng pellets despite the free availability of food and water. The preference for ginseng pellets over placebo pellets equated for most physical and nutritional properties suggests monkeys were seeking pharmacological effects. Behavior resulting from ingestion of ginseng pellets included hyperactivity and increased responding on the lever during all components of the schedule. This indicates that central nervous system stimulation may be the major pharmacological effect underlying self-administration here.

The monkeys tended to earn and ingest several ginseng pellets during the early part of each daily session and in subsequent periods 5 to 7 hours apart. This resulted in increased operant responding on the lever during ITI and early FI periods when the monkeys were required by training to with hold responding. Such patterns of responding can be viewed as disruption of stimulus control and are typically observed in the self-administration of psychomotor stimulants like cocaine and amphetamine. The pattern of spaced responding 5 to 7 hours apart is also typical of the manner in which monkeys will work for stimulant drugs. Taken together, these results are consistent with previous animal studies demonstrating stimulant effects on psychomotor performance from ginseng (Brekhman & Dardymov, 1969; Takagi, Saito & Tsuchiya, 1974).

When given unlimited access to ginseng pellets, monkeys earned and ingested approximately 10 g of ginseng root powder per day. These findings are consistent with previous studies with orally administered stimulants wherein monkeys titrated daily intake (Siegel, Johnson, Brewster & Jarvik, 1976). However, the individual dosage of ginseng root powder taken here averaged 1.2g/kg, an extremely high dosage when compared to human clinical dosages. Comparable high dosages in man have resulted in insomnia, depression, and nervous disorder (Keys, 1976). High dosages in animals are sometimes associated with disruption of performance (Petkov, 1978) and the findings here of increased ITI responding are consistent with this observation. Sereral experimenters have found an inhibitory or sedative effect from large dosages (e.g., Hong et al., 1974). While such sedative effects were not directly observed in the present study, they may help to explain the long intervals of 5 to 7 hours separating episodes of ginseng self-administration.

While the precise stimulus effects which reinforce self-administration of ginseng will need further clarification, this animal model should prove useful in future experimental investigations.

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