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# Consumption of palatable food decreases the anorectic effects of serotonergic, but not dopaminergic drugs in baboons ☆

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ABSTRACT

We examined the effects of periodic access to a palatable, high sugar content food (candy) in 8 male baboons on the anorectic response to D-amphetamine, which increases dopamine, and dexfenfluramine, which increases serotonin. During candy access, up to 200 candies containing 75% of energy as sugar were available during the morning on Mondays, Wednesdays and Fridays; food pellets (19% of energy as sugar) were available in the afternoon and throughout the remaining days of the week. During candy access, baboons consumed a mean of 177 pieces of candy containing 696 kcal (2.91 MJ) in the morning compared to 44 food pellets and 150 kcal (0.63 MJ) in the morning on non-candy days. Food pellet intake was lower during candy access. Complete dose–response functions for the effects of the drugs on food pellet intake on days that candy was not available were determined before, during, and after the period of access to candy. Dexfenfluramine and amphetamine produced dose-dependent decreases in food pellet intake and increases in latency to eat food pellets before, during, and after candy access. During access to candy, the dose–response function for dexfenfluramine was shifted to the right indicating the development of tolerance, while that for amphetamine was shifted to the left indicating sensitization. Only the dose–response function for dexfenfluramine returned to baseline after candy access suggesting that the difference was specific to concurrent palatable food consumption. We hypothesize that tolerance to the effects of dexfenfluramine reflects a decrease in the satiating effect of serotonin release due to repeatedly eating large amounts of palatable food.



## 1. Introduction

Behavioral similarities between excessive drug use, i.e., drug abuse and excessive food consumption, i.e., food abuse has long been noted [1], and a range of studies, mostly accomplished in laboratory rodents, highlight neurochemical and physiological similarities in drug abuse and overeating. For example, intermittent consumption of large amounts of palatable food that increases dopamine release can produce similar changes in brain chemistry as the repeated use of a drug that also increases dopamine release [2]. Consumption of sucrose plus chow increased the place preference conditioned by amphetamine [3], suggesting that diet increased the rewarding efficacy of dopaminergic compounds. Further, in another study [4] when rats self-administered oral amphetamine and had access to granulated sucrose and rat chow, their amphetamine intake decreased compared to when they access to chow alone. One interpretation of these findings is that sucrose and amphetamine were functioning as economic substitutes for each other [5]; an effect we have observed in non-human primates [6,7]. In several studies, propensity to drink sucrose solutions was correlated with larger locomotor responses to amphetamine [8], or propensity to acquire amphetamine self-administration [9]. Several studies have also demonstrated cross-sensitization between sugar and amphetamine [10,11].

It is a bit surprising that little data exist on the effects of dietary manipulations on the response to serotonergic drugs. Furthermore, the data that do exist are contradictory. An early study [12] failed to see an effect of a high sucrose diet on the anorectic effects of the serotonin releaser dexfenfluramine in rats. Another research group, however, has observed an attenuated behavioral response, e.g., paw treading, of the direct serotonin 1-A receptor agonist 8-hydroxy-N, N-dipropyl-2-aminotetralin (8-OH-DPAT) following consumption of a diet high in sucrose in rats [13,14], hypothesized to be related to serotonin receptor desensitization [15,16].

Because the data obtained in rodents clearly shows that diet can affect response to drugs, but the direction of change varies across studies and drugs, in this study we compared the effect of a dietary manipulation on the anorectic effects of the serotonergic drug dexfenfluramine and the dopaminergic drug D-amphetamine in non-human primates.

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A serotonergic and a dopaminergic drug were chosen based on suggestions that these 2 neurotransmitters affect different aspects of feeding behavior. An increase in serotonin, as caused by dexfenfluramine [17], has been hypothesized to be vital for the development of satiation [see 18 review]. An increase in dopamine, as caused by amphetamine [19], has been hypothesized to decrease hunger. If consumption of large amounts of a single macronutrient specifically affects hunger or satiation by altering the body's response to food even in the absence of the macronutrient, it may in turn alter the response to pharmacological manipulations that affect hunger and satiation.

In order to investigate how altering macronutrient intake can alter the response to a drug it is important to have procedures that generate excessive intake of that nutrient. Rodents avidly consume sucrose and fat. If given access to fat [20] or sucrose [21] during a part of the day when rats normally eat little (light cycle), they will eat large amounts of fat or sucrose. The sugar or fat consumption increases total energy intake, alters macronutrient contribution to intake and disrupts the pattern of feeding [see review 22]. Rats given access to fat for 2 h/day (3 h before the dark cycle) 3 days per week eat massive amounts of fat during those 2 h [23,24]. We have adapted these procedures to generate "binge" consumption of food high in fat or sugar in baboons [25,26]. When free-feeding baboons are given access to a preferred candy food item in the morning 3 days a week they derive as much energy from that item in a single "meal" as they do from the standard diet the remainder of the day [26]. Thus, the procedures not only generated excessive intake of a sugar-based candy, but because the candy was only available intermittently, it modeled periodic over-consumption of treats or snack foods.

In the present study, a complete dose–response function for the effects of D-amphetamine, which increases dopamine levels, and dexfenfluramine, which increases serotonin levels on food pellet consumption was determined before, during and after an 8-week period of access to a high-sugar candy 3 days a week. We used a procedure that allowed baboons to earn 20 candies once every 15 min over 2 h each morning (200 max). Baboons could then consume pellets during 4 possible afternoon meals, with number of meals and the size of each meal determined by each baboon. Although the baboons were not food deprived, other than during the dark cycle, the procedure limited the variability in the pattern of food intake. Limiting the rate of food intake by forcing breaks between eating the 20 candies has been shown to provide an eating baseline that was sensitive to the hypothesized effects of drugs on satiation [27].

The repeated administration of amphetamine to baboons results in the development of tolerance to its anorectic effects [28], i.e., the dose–response function determined during repeated administration was shifted to the right of the dose–response function determined before or after repeated administration. There was no evidence of cross-tolerance between dexfenfluramine and amphetamine [28]. Other studies have shown that rats who are tolerant to the effects of amphetamine on feeding behavior are cross-tolerant to the effects of other dopaminergic stimulant drugs [e.g., 29], indicating that drug exposure produced long-term changes in specific neurotransmitter function. We hypothesized that candy consumption 3 days a week would function as a drug does on central neurotransmitters altering brain response to other pharmacological manipulations, even in the absence of candy. Thus, we predicted that the dopaminergic drug, amphetamine, would produce smaller decreases in pellet intake when baboons were eating palatable food. In contrast, we predicted that the decrease in food intake caused by the serotonergic drug, dexfenfluramine, would not be affected by palatable food.

## 2. Method

### 2.1. Animals

Eight experimentally naïve adult male baboons (*Papio cynocephalus anubis*), initially weighing 17.5 to 23.1 (mean = 19.9) kg were individually housed in custom-designed non-human primate cages (0.94 × 1.21 × 1.52 m high) at The New York State Psychiatric Institute. The room was illuminated with fluorescent lighting from 7:00 AM to 7:00 PM daily. In addition to food and candy earned during experimental sessions, two chewable vitamins, two pieces of fresh fruit, and a dog biscuit were also given daily. Water was available *ad libitum* from a spout located at the back of each cage. All aspects of animal maintenance and experimental procedures complied with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals, and were approved by the New York State Psychiatric Institute Animal Care and Use Committee.

### 2.2. Apparatus

A response panel holding, from bottom to top, a food hopper, 2 pull-type, "Lindsley" response levers spaced 0.30 m apart (Gerbrands, Arlington, MA), 4 stimulus lights (two above each lever), and 2 pellet dispensers (BRS-LVE model PDC-005, Beltsville, MD) was attached to the front of each cage. All schedule contingencies were programmed using Pascal on Macintosh (Cupertino, CA) computers located, along with the interface, in an adjacent room.

### 2.3. Brief morning candy and food pellet sessions (responding on right lever)

There were 10 brief sessions beginning each day at 9:00 AM at 15 min intervals (Table 1). The beginning of each session was signaled by illumination of the right light above the right lever. The first pull on the right lever started a 6 min timer. During that interval each time the right lever was pulled 10 times both lights above the right lever flashed 10 times. The first time the baboon pulled the lever 10 times after 6 min had elapsed the left light above the right lever was illuminated. The next time the right lever was pulled 10 times 10 food pellets (Table 1) were delivered accompanied by the flashing lights. When candy was available 10 to 20 pieces of original fruit-flavored Skittles® candy were delivered. Baboons had 15 min to respond during each brief session. Failure to complete the minimum number of lever presses in 15 min terminated that brief session. If the baboon earned his pellet or candy deliveries in less than 15 min, no lights would be illuminated until the start of the next brief session.

### 2.4. Pellet meals (responding on left lever)

Pellet meals were available once at 7:00 AM each morning and 4 times in the afternoon (Table 1). Pellet meal availability was signaled by the illumination of the right light over the left lever. If a baboon wanted to eat a meal of pellets it had to pull the left lever. The first pull on the left lever started a 30 min a timer. During that interval each time the left lever was pulled 10 times both lights above the left lever flashed 10 times. The first time the baboon pulled the lever 10 times after 30 min had elapsed, the left light above the left lever was illuminated. Each time the left lever was then pulled 10 times baboons received 1 food pellet accompanied by the flashing lights. There was a 10 s interval after each pellet delivery when responding was not counted. Pellet meals ended when the 90 min session terminated or when the baboon stopped responding for 10 min. As with the brief sessions, baboons had the option to not respond.

### 2.5. Procedure

After baboons acclimated to the housing conditions, they were trained to respond for food pellets under the conditions described above i.e., 10 brief sessions in the morning and opportunities for a pellet meal through the day, except overnight when baboons rarely eat. Once responding for pellets was stable (no upward or downward trends in pellet intake) complete dose–response functions were determined for