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Effects of Diet on Sensitization to Cocaine-Induced Stereotypy in Female Rats

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SHUMSKY, J. S., P. L. SHULTZ, J. TONKISS AND J. R. GALLER. *Effects of diet on sensitization to cocaine-induced stereotypy in female rats.* PHARMACOL BIOCHEM BEHAV **58**(3) 683–688, 1997.—The progressive increase in cocaine-induced stereotyped behavior that accompanies repeated cocaine injections (sensitization) was examined in rats consuming different diets. Adult female Sprague–Dawley rats were fed one of three diets: low protein (6% casein), adequate protein (25% casein), or a standard chow diet. Following 1 week of adaptation to the diets, the rats were injected every 3–4 days with either cocaine (30 mg/kg, IP) or saline, and the total amount of stereotypy was measured over a 90-min interval following each of four injections. Cocaine-induced stereotypy peaked at 40–50 min following each injection, after which it declined for all diet groups. With repeated injections, the total amount of stereotypy increased in all diet groups. By the fourth injection, the low protein diet group (6% casein) exhibited a slower onset and a possibly prolonged duration of cocaine-induced stereotypy when compared with the two adequate protein diet groups (25% casein and chow). Interestingly, the rats in the two purified diet groups (6% casein and 25% casein) exhibited significantly more stereotypy across injections than those in the chow diet group. Weight differences did not explain the differences in stereotypy present among the diet groups. This study concludes that diet significantly alters the pattern of cocaine-induced stereotypy in female rats, especially after repeated exposure. © 1997 Elsevier Science Inc.

Cocaine Diet Malnutrition Protein restriction Rat Sensitization Stereotypy

IT has been demonstrated that the actions of drugs can be influenced greatly by nutritional factors [reviewed in (1,3,7)]. For instance, in clinical subjects switched from a high-carbohydrate/low-protein diet to one that was low carbohydrate/high protein, the rate of clearance of the drug propranolol was found to be increased, suggesting that the former diet had an inhibitory effect on hepatic drug metabolism (6). A reduction in drug-metabolizing enzyme activity has also been proposed to account for the increased half lives of chlorothiazide—a commonly used diuretic (9)—and pentobarbital (10), under conditions of protein deprivation in rats. Dietary fat content also has a significant influence on drug action. Diets high in saturated fat have been shown to enhance and prolong the analgesic action of morphine compared to animals fed a regular chow diet (13) and delay the development of tolerance to the anorectic effect of amphetamine compared to animals fed a high-carbohydrate diet (16).

Recently, we developed an animal model of prenatal cocaine exposure in which rats were exposed to both cocaine and a protein-restricted diet for 5 weeks prior to mating and throughout pregnancy (26,27). Given the poor nutritional status of drug-addicted individuals (24) and the chronic nature of their drug exposure, this model was devised to more accurately reflect these aspects of the clinical picture. The dietary control animals for this model were fed either a purified diet of higher protein content (having the same high fat content as the low protein diet, but a lower level of carbohydrate), or a chow diet (having a high protein content but a lower fat content than either of the other diets). The known importance of nutrition to drug action prompted the current study in which the behavioral response to cocaine was documented in the females as they adapted to the various diets during repeated drug injections. Diet-related differences in drug response may indicate the potential for a different pattern of drug exposure

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in their fetuses when subsequently mated. The behavior selected for quantification was cocaine-induced stereotypy (repetitive body movements, e.g., head-bobbing) because the time of onset, peak and offset of such behaviors have been closely correlated with the rate of metabolism of the drug (5).

Using our animal model of prenatal cocaine exposure, the repeated IP administration of cocaine prior to mating was observed to progressively increase the amount of stereotypy displayed. This process is known as sensitization or reverse tolerance (20,29) and has previously been documented with respect to both stereotypy (5,14,15,19,22,23) and spontaneous locomotor activity (23,28). To our knowledge, no previous studies have examined the effects of dietary composition on sensitization to cocaine as determined by analysis of stereotyped behaviors. Consequently, the present study was designed to examine the effect of a low-protein diet, a diet of adequate protein content, or a laboratory chow diet on the acute behavioral response to cocaine and the overall pattern of behavioral sensitization to this drug.

METHOD

Subjects

Thirty-six adult female, Sprague–Dawley (VAF plus) rats, purchased from Charles River Laboratories (Kingston, MA), served as subjects. The rats weighed 175–200 g and were approximately 70 days old at the start of testing. Each subject was individually housed in animal quarters that were kept at a temperature of 73 ± 3°F with 50 ± 5% humidity on a reverse 12-h light/dark cycle (lights on at 2000 h). Beginning 1 week prior to testing, subjects were acclimated to the housing facilities and given ad lib access to water and one of three diets (described below).

Nutritional and Drug Treatments

Rats were allocated to one of two purified pelleted diets (Teklad, Madison, WI) or a standard rat chow (Purina Mills, Inc., Richmond, IN; Formula 5001). The purified diets contained low protein (6% casein) or adequate protein (25% casein), and had the same high fat content (15.3%), but they differed in their protein content (5.3 or 21.8%, respectively). They were rendered isocaloric (4.22 kcal/g) by the addition of both simple and complex carbohydrate to the low-protein diet. A previous study has determined that these two diets are consumed in equal amounts among nonpregnant females (12), suggesting that they have similar palatability. These diets were supplemented with methionine to ensure a complete amino acid distribution and matched for vitamin and mineral content (25). The chow diet contained an amount of protein that was similar to the 25% casein diet (23.4%), but had a lower fat (4.5%) and calorie content (3.30 kcal/g). The fat in the purified diets was provided by corn oil, whereas the fat in the chow diet was derived from a mixture of animal and plant sources. Rats were provided with the diets for 1 week prior to the first of four injections given at 3–4-day intervals over a 2-week period (n = 12 per diet group). Rats in each diet group received either saline injections (n = 6) or 30 mg/kg cocaine injections (n = 6). Cocaine hydrochloride (supplied by NIDA) dissolved in 0.9% isotonic saline was injected intraperitoneally (IP) at a volume of 1 ml/kg. One rat in the chow-fed group did not respond to the cocaine injections and was eliminated from the study.

Behavioral Testing

Behavioral testing was conducted in home cages between 1300 and 1700 h under red fluorescent light. Behavior ratings were made 10 min before the animals received cocaine or saline injections and at each of nine 10-min intervals (bins) following drug administration. At each observation, two observers who were blind to the experimental group of the subjects rated each animal independently for 30 s. Inter-rater reliability of greater than 90% was maintained throughout the course of the study. The following stereotyped behaviors, which are known to be elicited by cocaine injection [e.g., (2,4,21)]: compulsive sniffing, rearing, head bobbing, forepaw treading, weaving, and oral dyskinesias (e.g., licking, biting, gnawing) were identified and scored on an intensity scale (0 = no stereotyped behavior, 1 = mild, 2 = moderate, or 3 = intense). Each behavior was assigned a score by averaging the ratings of the two observers at each time interval.

Data Analysis

Body weights for all six groups of animals were analyzed by a three-way (diet × drug × injection number) analysis of variance (ANOVA) with injection number taken as a repeated measure. As expected, stereotyped behaviors were observed with extremely low incidence following saline injection, precluding inclusion of the saline-treated animals in the statistical analysis. Thus, only stereotypy data from the three groups receiving cocaine injection were subsequently analyzed. A three-way ANOVA (diet × injection number × bin) was performed with both Injection number and bin taken as repeated measures. Separate two-way ANOVAs (diet × bin) were performed for each injection to identify the source of higher order interactions obtained within the overall analysis. Typically, individual cocaine-elicited stereotyped behaviors are analyzed rather than a total score; therefore, the four behaviors used to create the total stereotypy score (compulsive sniffing, rearing, head bobbing, and forepaw treading) were also analyzed individually by three-way ANOVA (diet × bin × injection number) with both injection number and bin taken as repeated measures. To characterize the results following injection #4 (during the greatest degree of sensitization), subsequent analyses were performed using two-way ANOVAs (diet × bin). Post hoc comparisons were made using Tukey's test where indicated by ANOVA.

RESULTS

Body Weight

Figure 1 shows that body weight significantly increased in all three diet groups. Three-way ANOVA (diet × drug × injection number) indicated a significant effect of injection number, $F(3, 90) = 248.5$, $p < 0.001$. However, body weight differed among the diet groups over the course of the experiment [diet × injection number: $F(6, 90) = 8.1$, $p < 0.001$]. At the time of the first injection, the 6% casein group weighed significantly less than the other two groups, which were of similar weight. As testing progressed, body weight was least in the 6% casein group and greatest in the 25% casein group with the chow-fed rats being intermediate. By injection #4, each group was significantly different from the other (25% casein > chow > 6% casein; Tukey's test, $p < 0.05$). Hence, a significant overall effect of diet was indicated by ANOVA, $F(2, 30) = 14.3$, $p < 0.001$, but there was no effect of Drug

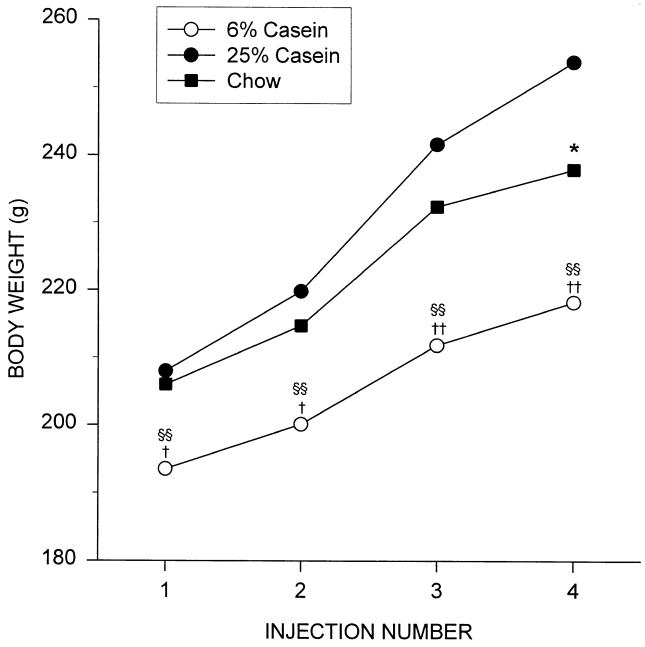

FIG. 1. Effect of diet on body weight. Data shown are the mean body weight for the three diet groups. Because ANOVA showed no effect of drug, the weights of both cocaine and saline treated rats were combined for the purposes of analysis and presentation (n = 36), although the figure is representative of data from the cocaine treated group. 6% casein vs. 25% casein (§§$p < 0.01$); 6% casein vs. chow (††$p < 0.01$; 25% casein vs. chow, *$p < 0.05$).

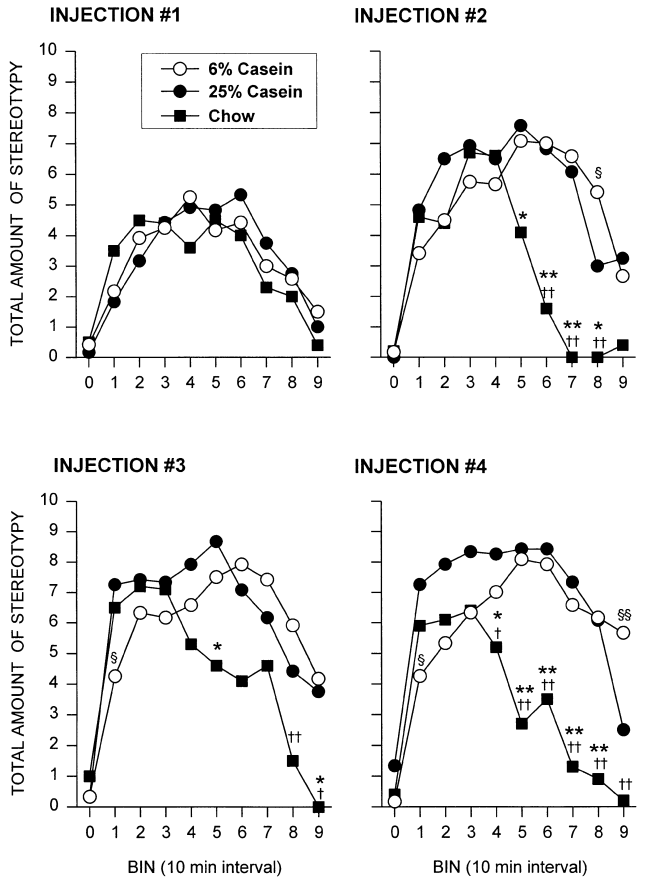

FIG. 2. Total amount of stereotypy. Data shown are the mean total amounts of stereotypy for each of the three diet groups: 6% casein (n = 6), 25% casein (n = 6), and chow (n = 5), following the four cocaine injections across nine 10-min bins. 6% casein vs. 25% casein (§$p < 0.05$, §§$p < 0.01$); 6% casein vs. chow (†$p < 0.05$, ††$p < 0.01$); 25% casein vs. chow (*$p < 0.05$, **$p < 0.01$).

(i.e., saline-injected rats weighed the same as cocaine-injected rats) and no interaction involving drug treatment.

Total Stereotypy Scores

The six cocaine-elicited behaviors occurred with varying frequency in the overall data set, specifically: compulsive sniffing (31%), rearing (23%), head bobbing (22%), forepaw treading (18%), weaving (5%), and oral dyskinesias (1%). Because of their low incidence, the latter two behaviors were omitted from the data analysis. The total amount of stereotypy was determined in each 10-min bin by summing the scores from the remaining four behaviors.

Figure 2 illustrates the total amount of stereotypy observed in the three diet groups across bins for each of the four injections. In general, the total amount of stereotypy changed across bins, $F(9, 126) = 72.3$, $p < 0.001$. As shown in the figure, the behavioral response rose to a peak effect and then declined within the 90-min observation interval. A significant main effect of injection number, $F(3, 42) = 27.6$, $p < 0.001$, was revealed as the overall means of the total stereotypy scores increased over Injections #1–3 (mean = 3.13, 4.36, 5.36, respectively), and reached a plateau at Injection #4 (mean = 5.31). Additionally, a significant interaction was found for injection number × bin, $F(27, 378) = 2.4$, $p < 0.001$] indicating a shift in the pattern of drug effect over repeated injections as would be expected with the development of sensitization. A main effect of diet, $F(2, 14) = 7.1$, $p < 0.01$, was also indicated but the presence of higher order interactions involving diet [diet × injection number × bin: $F(54, 378) = 2.4$, $p < 0.001$; diet × injection number: $F(6, 42) = 3.8$, $p < 0.01$; diet × bin: $F(18, 126) = 7.8$, $p < 0.001$] suggested a complex influence of diet on cocaine-induced stereotypy. To facilitate interpretation of the data, behavioral data for each individual injection were considered separately.

Injection #1. ANOVA revealed a significant effect of bin, $F(9, 126) = 31.4$, $p < 0.001$. As illustrated in Fig. 2, the behavioral effect of cocaine increased to a peak and then declined. However, there was no significant effect of diet and no diet × bin interaction, indicating that the behavioral effect of cocaine was initially similar among the three diet groups.

Injection #2. ANOVA revealed a significant effect of bin, $F(9, 126) = 28.5$, $p < 0.001$. In addition, differences emerged between diet groups, $F(2, 14) = 9.6$, $p < 0.01$, along with a significant diet × bin interaction, $F(18, 126) = 5.6$, $p < 0.001$. Post hoc analysis indicated that the chow diet group showed significantly less total stereotypy than the 25% casein diet group ($p < 0.05$) during bins 5–8, and significantly less total stereotypy than the 6% casein diet group ($p < 0.01$) during bins 6–8. Furthermore, the 6% casein diet group showed significantly more total stereotypy than the 25% casein diet group ($p < 0.05$) during bin 8.

Injection #3. ANOVA again indicated the effect of bin, $F(9, 126) = 27.0$, $p < 0.001$. No main effect of diet was found. However, a significant diet × bin interaction, $F(18, 126) = 3.3$, $p < 0.001$, indicated the continued presence of diet-related differences. Post hoc analysis confirmed that the chow diet group showed significantly less total stereotypy than the 25% casein diet group ($p < 0.05$) during bins 5 and 9, and significantly less total stereotypy than the 6% casein diet group ($p < 0.01$) during bin 8. Furthermore, the 6% casein diet group showed significantly less total stereotypy than the 25% casein diet group ($p < 0.05$) during bin 1.

Injection #4. ANOVA again revealed the effect of bin, $F(9, 126) = 37.0$, $p < 0.001$. Diet-related differences in the behavioral effect of cocaine were evident as indicated by a significant effect of diet, $F(2, 14) = 13.6$, $p < 0.001$, and a significant diet × bin interaction, $F(18, 126) = 7.2$, $p < 0.001$. Post hoc analysis confirmed that the chow diet group showed significantly less total stereotypy than the 25% casein diet group ($p < 0.05$) during bins 4–8, and significantly less total stereotypy than the 6% casein diet group ($p < 0.05$) during bins 4–9. Furthermore, the 6% casein diet group showed significantly less total stereotypy than the 25% casein diet group ($p < 0.05$) during bin 1 and significantly more total stereotypy than the 25% casein diet group ($p < 0.01$) during bin 9.

In summary, the present results demonstrate that differences in the total amount of stereotypy between diet groups developed over repeated cocaine injections (i.e., during sensitization). Diet-related differences emerged by the second injection; in which the chow diet group showed less total stereotypy than either of the purified diet groups (6 or 25% casein), particularly in the later bins. By the third injection the 6% casein diet group exhibited less total stereotypy at bin 1, and by the fourth injection the 6% casein diet group showed more total stereotypy at bin 9 than either of the higher protein diet groups (25% casein or chow).

Individual Stereotyped Behaviors

The data from the four stereotyped behaviors were also analyzed separately across injections. ANOVAs revealed significant three-way interactions [diet × injection number × bin] for compulsive sniffing, $F(54, 378) = 2.3$, $p < 0.001$, rearing, $F(54, 378) = 1.3$, $p < 0.10$], head bobbing, $F(54, 378) = 1.4$, $p < 0.05$, and forepaw treading, $F(54, 378) = 1.5$, $p < 0.05$. To explain these higher order interactions, the data from the individual behaviors were subsequently analyzed at injection #1 (initial response) and injection #4 (maximal sensitization). Consistent with the results from the total stereotypy analysis, no effects of diet were associated with any of the behaviors following injection #1 (data not shown). However, as illustrated in Fig. 3, many differences emerged following injection #4 and these are described below.

Compulsive sniffing. A significant diet × bin interaction, $F(18, 126) = 6.0$, $p < 0.001$, and a significant main effect of bin, $F(9, 18) = 29.9$, $p < 0.001$, and of diet, $F(2, 14) = 12.4$, $p < 0.001$, were found. Post hoc analysis revealed that the chow diet group exhibited less compulsive sniffing than the 6% casein diet group at bins 5–9 ($p < 0.05$) and less compulsive sniffing than the 25% casein diet group at bins 5–9 ($p < 0.01$). Furthermore, the 6% casein diet group showed significantly more stereotypy than the 25% casein diet group ($p < 0.05$) during bin 9.

Rearing. There was a significant diet × bin interaction, $F(18, 126) = 2.8$, $p < 0.001$, and a significant main effect of bin, $F(9, 18) = 6.6$, $p < 0.001$, but not of diet. Post hoc analysis revealed only that the chow diet group exhibited more rearing than the 6% casein diet group at bin 1 ($p < 0.05$) and less rearing than either the 6% or the 25% casein diet groups only at bin 8 ($p < 0.05$).

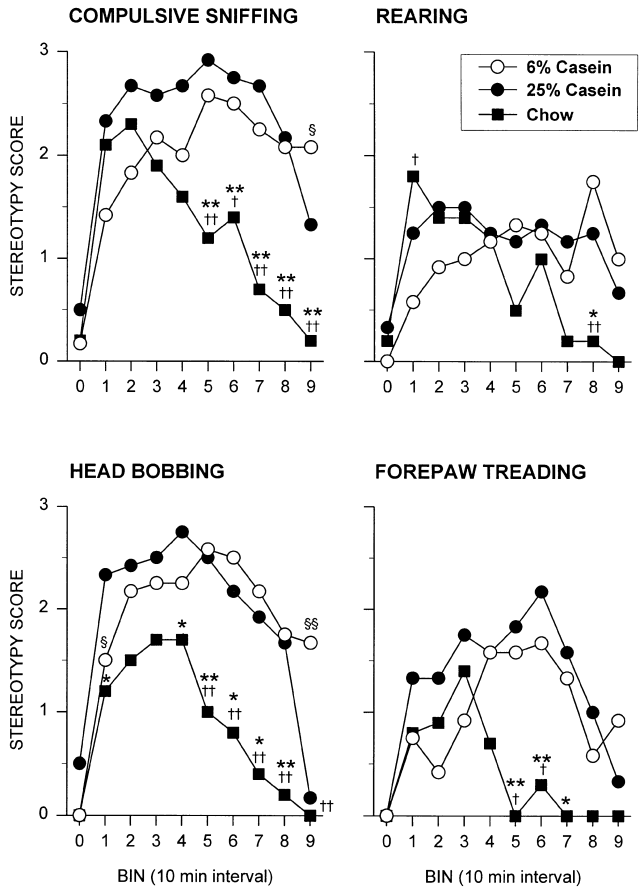

FIG. 3. Individual stereotyped behaviors following injection #4. Data shown are the mean stereotypy scores for each of the four stereotyped behaviors elicited by the fourth cocaine injection for each of the three diet groups: 6% casein ($n = 6$), 25% casein ($n = 6$), and chow ($n = 5$). 6% casein vs. 25% casein (§$p < 0.05$, §§$p < 0.01$); 6% casein vs. chow (†$p < 0.05$, ††$p < 0.01$); 25% casein vs. chow (*$p < 0.05$, **$p < 0.01$).

Head bobbing. A significant diet × bin interaction, $F(18, 126) = 3.6$, $p < 0.001$, and a significant main effect of bin, $F(9, 18) = 28.2$, $p < 0.001$, and of diet, $F(2, 14) = 11.4$, $p < 0.001$, were found. Post hoc analysis revealed that the chow diet group exhibited less head bobbing than the 6% casein diet group at bins 5–9 ($p < 0.01$) and less head bobbing than the 25% casein diet group at bins 4–8 ($p < 0.05$). Furthermore, the 6% casein diet group showed significantly less stereotypy than the 25% casein diet group ($p < 0.05$) during bin 1 and significantly more stereotypy than the 25% casein diet group ($p < 0.01$) during bin 9.

Forepaw treading. A significant diet × bin interaction, $F(18, 126) = 2.7$, $p < 0.001$, and a significant main effect of bin, $F(9, 18) = 8.1$, $p < 0.001$, and of diet, $F(2, 14) = 6.9$, $p < 0.01$, were found. Post hoc analysis revealed that the chow diet group exhibited less forepaw treading than the 6% casein diet group at bins 5–6 ($p < 0.05$) and less forepaw treading than the 25% casein diet group at bins 5–7 ($p < 0.05$).

In summary, other than for rearing, these patterns of behavioral response were consistent among the individual behaviors. Rats in the 6 and 25% casein diet groups exhibited similar patterns of response in their individual stereotyped behaviors, although scores from the 6% casein diet group were lower than those from the 25% casein diet group except for the later bins. The chow-fed rats exhibited a distinctly different pattern in that their stereotypy scores peaked and declined more rapidly compared to the other two groups.

DISCUSSION

The aim of this study was to examine the effect of three different diets on the initial response to cocaine and the development of sensitization to this drug, as measured by stereotyped behavior in female rats. After the first injection, the response to cocaine was not significantly different among the three diet groups. Within this session the total amount of stereotypy increased (bins 1–5), peaked, and then declined (bins 6–9). With repeated injections, the total amount of stereotypy increased across injections and the time to reach maximal (peak) effect decreased across injections, providing evidence that behavioral sensitization occurred using the present procedure. Additional analysis of individual stereotyped behaviors, especially head bobbing and compulsive sniffing, showed similar patterns to those indicated by the overall analysis. Although the present findings are consistent with previous reports demonstrating behavioral sensitization to repeated IP cocaine injection in chow-fed female rats [e.g., (5,15,18)], diet clearly influenced the development of sensitization to cocaine by altering the temporal pattern and total amount of stereotyped responses after multiple injections. This difference was greatest when comparing rats fed the chow diet to rats fed either of the two purified diets. As early as the second cocaine injection, the total amount of stereotypy peaked then declined more rapidly in the chow-fed diet group than in the two purified diet groups. Rats in the 6% casein diet group had a reduced amount of cocaine-induced stereotypy in bin 1 compared with rats in the 25% casein diet group by the second injection, indicating a slower onset of the drug effect. Following the fourth injection, the total stereotypy score was significantly greater for the 6% casein diet group than the 25% casein diet groups in bin 9. These results may suggest a prolonged duration of drug effect in the 6% casein diet group, but because this is based upon a single data point, such an interpretation must remain tentative.

An interesting feature of these results was that no differences existed between the three dietary groups in their behavioral response to the first cocaine injection, but that a difference emerged with repeated injections. One interpretation is that dietary composition affected the development of sensitization to cocaine but not the response to an acute administration (i.e., when they were drug naive). However, because the procedure adopted for use in the present investigation was exactly the same as that used in our prenatal cocaine model (26,27), the response to successive drug injections was confounded with the length of time the rats had been exposed to the diet. This raises the possibility that different behavioral responses to the drug emerged as a consequence of the more prolonged dietary exposure. Although this interpretation cannot be ruled out entirely, a small control study (unpublished findings) failed to reveal any behavioral differences across these various dietary conditions in response to an acute injection of cocaine administered following 2 weeks of adaptation to the diets, suggesting that the repeated exposure to cocaine was the critical factor in dissociating between the drug response of the dietary groups in the present experiment.

The question that now arises is what are the critical differences between diet groups that might have generated the behavioral differences in response to repeated cocaine injections? Specifically, delayed onset of stereotypy in 6% casein rats compared with 25% casein rats (and possibly a delayed offset), and both lower total amounts of stereotypy and a more rapid decline in stereotypy after the peak effect in rats on the chow diet compared with those administered the purified diets. The 6% casein diet was designed to be relatively low in protein, while the 25% casein diet was designed to be high in protein, such that pregnant rats would receive either an insufficient or adequate supply of this nutrient respectively (17). However, to ensure equal caloric density, carbohydrate (in the form of starch and simple sugars) was added to the 6% casein diet. Thus, the 6% casein diet can be described as low protein/high carbohydrate and the 25% casein diet high protein/low carbohydrate. The delayed onset of cocaine-induced stereotypy in rats on the low-protein/high-carbohydrate diet is probably related to a slower absorption and/or distribution of the drug leading to initially lower levels of cocaine in the brain. However, a pharmacokinetic analysis would be necessary to determine whether this is the case. The tendency for a more prolonged drug action in the females provided the low protein diet may be due to reduced levels of drug metabolism. There is support for this idea in the finding that low levels of dietary protein increase the half life of various drugs (9,10), which is attributable to a reduced activity of drug-metabolizing enzymes (3). It is of note that the present findings of prolonged drug action in rats with a low-protein/high-carbohydrate diet is similar to that seen in human subjects (6), albeit that this observation was made with a different class of drugs.

The most dramatic finding in the current study was the large difference between the chow diet group and those fed the purified diets. The main difference between these diets is the amount of fat and its source. The purified diets possess more than three times the quantity of fat than the chow diet (15.3% cf. 4.5%). Corn oil serves as the sole source of this fat in the purified diets (i.e., it is unsaturated), whereas the fat in the chow diet is derived from both plant and animal sources (i.e., saturated and unsaturated fats). Both the quantity and composition of dietary fats have been shown to exert significant influences on drug action. Diets high in saturated fat enhance and prolong the analgesic effect of morphine (13) compared to rats fed a normal chow diet, and these diets significantly delay the development of tolerance to the anorectic effect of amphetamine (16) and enhance the acute anorectic effect of fenfluramine (11) compared to rats fed a high-carbohydrate diet. Both the chow diet and high-carbohydrate diets in those studies had lower amounts of fat. Dietary fat composition has also been shown to influence drug action. Pentobarbitone-induced sleeping time was significantly prolonged in rats fed a high saturated fat diet (lard) compared with rats fed a diet high in unsaturated fat (sunflower seed oil) (8). Given these findings, the enhanced and prolonged behavioral response to cocaine in rats fed the purified diets compared to the chow fed controls appears to be best explained by the difference in total amount of fat rather than its composition, although other possibilities cannot be overlooked. For example, the purified diets and chow diet also differ in their source proteins (casein vs. a variety of natural sources), and it is not known how this dietary difference might affect the action of cocaine.

Dietary composition also influenced the body weight of the rats, raising the possibility that differential drug effects were contingent upon the different body sizes. However, there was no simple relationship between body weight and the observed drug effect. For example, rats in the 25% casein diet group weighed the most and rats in the 6% casein diet group weighed the least, but both groups exhibited higher amounts of stereotypy than the chow-fed rats whose body weight was intermediate.

The implications of the present findings for our ongoing research on prenatal cocaine are twofold. First, the 25% casein diet group is the only correct dietary control group by which to compare the 6% casein group owing to the marked difference in response to cocaine exhibited by the chow diet group. Second, the small differences present in the 6% casein group compared to the 25% casein group suggest the potential for differential drug experience in the malnourished fetuses when these females are eventually mated. Such differences may be important for brain development, function, and behavior.

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