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Iron deficiency in rats decreases acquisition of and suppresses responding for cocaine

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Abstract

Iron deficiency impairs nigrostriatal and mesolimbic dopamine systems by causing decreased densities of D_1 and D_2 receptors and the dopamine transporter in the terminal fields, caudate–putamen and nucleus accumbens. Iron deficiency also causes deficits in dopamine-related pharmacological indices, e.g., deficits in locomotor stimulation by cocaine and locomotor inhibition by raclopride. Based on this knowledge, we hypothesized that iron deficiency would have a major impact on cocaine self-administration. Male Sprague–Dawley rats were fed an iron-deficient diet starting at weaning (Day 21) and continuing throughout the experiment. At 57–58 days of age, all animals had catheters implanted surgically into the jugular vein. Approximately 2 weeks later, all animals were trained to lick an empty spout for intravenous cocaine, delivered by infusion pump at 0.33 mg/kg. During the course of training, all animals acquired intravenous cocaine self-administration, however, the course of acquisition was significantly slower for the iron-deficient animals. When tested for responding on a progressive ratio (PR) schedule, the control animals maintained a constant number of infusions, whereas the responding of the iron-deficient animals fell off sharply. When the dose of cocaine was decreased, control, but not iron-deficient animals adjusted the amount administered by increasing the number of infusions. Finally, the failure to respond by the iron-deficient animals was not simply due to a failure to lick (i.e., a motor impairment), because both the iron-deficient and the control animals emitted approximately 1000 licks/20 min session when given free access to a palatable 0.1 M sucrose solution. Taken together, the data show that severe iron deficiency early in life can diminish the capacity of cocaine, but not sucrose to reinforce behavior. The question raised by this research thus, is whether iron deficiency alters hedonic-like responses only to dopamine-related behaviors and the degree to which willingness to "work" contributes to the effect.
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Keywords: Iron deficiency; Rats; Cocaine self-administration

1. Introduction

According to the World Health Organization, iron deficiency afflicts an estimated 2–4 billion people worldwide. In addition to causing anemia, iron deficiency affects most major organ systems, including the brain. The behavioral consequences of iron deficiency are pronounced in children and include lethargy, attentional and affective difficulties (Lozoff et al., 1987). Stimulus-response latencies for auditory evoked potentials in iron-deficient infants are also increased (Roncagliolo et al., 1998). In rats, iron deficiency produces behavioral disturbances (Piñero et al., 2001) similar to those seen in children, including decreased locomotion and increased anxiety-like behaviors (Beard et al., in press). Moreover, in rats, iron deficiency decreases expression of dopamine receptors and the transporter in the major projection areas of nigrostriatal and mesolimbic dopamine systems (Erikson et al., 2000, 2001). These observations are congruent with behavioral data (Beard et al., in press) and are further reinforced by our findings of decreased sensitivity to cocaine and raclopride, a dopamine D_2 antagonist (Erikson et al., 2001). A reasonable hypothesis thus is that iron deficiency in children may also affect their sensitivity to drugs that affect the central dopamine systems. Recently, we showed that iron deficiency in rats increased the ED_{50} for

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cocaine to stimulate locomotor activity and increased the ED_{50} for raclopride (a potent D_2–D_3 dopamine receptor antagonist) to inhibit locomotor activity (Erikson et al., 2000). These findings led us to hypothesize that iron deficiency may also affect cocaine self-administration. Caine and Koob (1994) showed that destruction of mesolimbic dopamine pathways abolished cocaine self-administration in rats but that temporary impairment of mesolimbic dopamine pathways (by dopamine receptor antagonists–partial agonists) inhibited cocaine self-administration at lower doses but actually increased the self-administration of cocaine at higher doses (Koob et al., 1987; Caine et al., 1995). In other words, destruction of mesolimbic dopamine pathways eliminates the reinforcing effect of cocaine but pharmacological impairment of these pathways only decreases the reinforcing effect, leading to subsequent behavioral compensation (i.e., self-administration of higher doses of the drug). Our working hypothesis was that iron deficiency in rats during the postweaning period of development and continuing through into young adulthood, would also impair the reinforcing effect of cocaine. Thus, we reasoned that iron-deficient animals would self-administer less cocaine than controls at lower doses but might self administer cocaine more readily as the dose increased.

2. Methods

2.1. Animals and diets

Sixteen male Sprague–Dawley rats were purchased from Harlan Sprague–Dawley (Charles River Laboratories) and divided into two groups. Beginning at 21 days of age, the control group ($n=8$) was fed an iron-adequate, powdered diet (35 ppm) and the experimental group ($n=8$), an iron-deficient (3.5 ppm) diet ad libitum. The diets (AIN-93G) were prepared according to the specifications of the American Institute of Nutrition as described by Reeves et al. (1993). The diets met all nutritional requirements with the exception of the iron content for the low iron diet. Twenty-four hours food consumption in grams was recorded for all animals and distilled water was made available from Nalgene cylinders fitted with silicone stoppers and stainless steel drinking tubes. All animals were maintained on a 12-h light–dark cycle with lights on at 07:00 h and the vivarium environment was maintained at 21 °C with humidity and ventilation automatically controlled. The subjects were weighed daily and 72 h prior to testing, a blood sample was taken from the tip of the tail to determine the effect of the diet on hemoglobin concentration. A similar sample was taken 48 h after the final day of testing.

2.2. Self administration catheter

As described by Grigson and Twining (in press), the catheters were custom made in our laboratory using a modified procedure described by Koob et al. (1987). The catheter consists of two pieces of Silastic tubing (0.012 in. ID, 0.025 in. OD, 14 cm long; 0.025 in. ID, 0.047 in. OD, 2.5 cm long: Baxter Scientific) attached to a stainless steel guide cannula bent at a 90° angle at one end (Plastic One, Item #C3136). The cannula/tubing assembly is molded into a permanent dental cement base using a custom-designed mold. A 2.5×2.5 cm piece of mesh (Small Parts) is permanently fixed to the base via dental cement and functions as a backplate for the catheter assembly. A small silicon rubber bubble is placed appropriately 3.5 cm from the end of the small tubing. The 3.5-cm length of tubing is placed in the jugular vein and anchored to muscle with surgical silk. The entire catheter is flushed with and then soaked in absolute alcohol for 24 h prior to implantation.

When the rats were between 57 and 58 days of age, they were anesthetized with ketamine (70 mg/kg)/xylazine (16 mg/kg) intramuscularly and the hair was shaved on in two places: (1) on the back of the rat between the shoulder blades and (2) directly on top of the jugular vein on the neck. One incision was made above the jugular vein at the neck (approximately 10 mm in length), at about a 30° angle away from the midline. Another incision was made on the dorsum of the rat (approximately 1 in. in length), horizontally positioned between and just below the shoulder blades. The skin was separated from the muscle in both locations using hemostats. The cannula was then pushed subcutaneously from the incision on the dorsum, over the right foreleg and through the incision on the ventrum of the rat. The catheter was inserted through the cannula, and then the cannula was removed. The rat was placed supine and the jugular vein exposed by gently separating the tissue surrounding the vein using blunt micro forceps. Once the jugular vein was located and cleared from surrounding tissue, a stainless steel rod (3 mm diameter) was moistened with saline and gently placed under the jugular vein. Once the rod was in place it was used to lift the vein to enable the experimenter to make a small incision (approximately 0.5 mm) in the vein. The catheter (0.025 in. OD side) was then inserted into the vein through the incision. Verification that the catheter was in the jugular vein was made by attaching a syringe filled with saline to the other end of the catheter (coming out the back of the rat) and drawing back blood through the syringe. Following verification, the catheter was secured into position by tying two ligatures around the vein and tubing both before and after the silicon rubber bubble. Once anchored, the skin was sutured closed and betadine antibiotic ointment (Baxter) applied topically. The rats were then treated intravenously with 0.8 cc of 16.6% tobramycin sulfate and 0.2 cc of 400 mg oxycillin sodium once a day for 5 days. For the remainder of the study, the catheters were flushed with a 0.2-cc saline/heparin solution in order to maintain catheter patency. Patency of the catheter was verified as indicated using 0.15 cc of 1% brevital administered intra-

venously. This procedure yields approximately a 75% success rate in which catheters remain patent for 2 months or longer.

2.3. Coupling assembly

Prior to the start of each self-administration session, a coupling assembly was anchored to the back of the rat to provide protected passage of the catheter tubing from the animal. The coupling assembly (a metal spring attached to a metal spacer with Tygon tubing inserted down the center) was attached to the catheter assembly. The catheter tubing was attached to a counterbalanced swivel device (Instech) that in turn was attached to a fluid injection assembly (syringe pump) outside the sound-attenuating cubicles. The fluid injection assembly enabled intravenous infusion of cocaine during self-administration sessions. In the animal's home cage, the catheter was sealed with a piece of Tygon tubing and a metal spacer placed over the catheter assembly.

2.4. Experimental chambers

The rats were trained in one of six identical modular operant chambers (Med Associates, St. Albans, VT) measuring $30.5 \times 24.0 \times 29.0$ cm (length $\times$ width $\times$ height) and housed in a light and sound attenuated cubicle. All chambers have a clear Plexiglas top, front and back wall. Sidewalls are made of aluminum. The grid floors consist of 19 4.8-mm stainless steel rods spaced 1.6 cm apart (center to center). Each chamber is equipped with two retractable sipper tubes that can enter the chamber through 1.3-cm diameter holes spaced 16.4 cm apart (center to center). A stimulus light is located 6 cm above each. In the extended position, the tip of the sipper tube is aligned in the center of the hole, flush with the right end wall. A lickometer circuit is used to monitor and record empty bottle licks. Each chamber is also equipped with a house light (25 W), a tone (Sonalert Time Generator, 2900 Hz) and a speaker for white noise (75 dB). Cocaine reinforcement is controlled by an electronic circuit that operates a syringe pump (Razel Scientific Inst., Model A). Control of events in the chamber and collection of the data are carried out on-line using a Pentium-based computer. Programs are written in the Medstate notation language (Med Associates).

2.5. Operant training and testing

Forty-eight hours before testing, all rats were placed on a water deprivation regimen in which they received 2 h access to de-ionized H_2O daily. The rats were then habituated to the chambers for 5 min a day for 3 days. During testing, two empty drinking tubes advanced, one on the right and one on the left of the chamber. The house light was turned off and a stimulus light was illuminated above the active spout.

2.5.1. Acquisition

The animals were subsequently trained on a FR_{10} schedule ab initio where completion of 10 licks on an empty spout lead to an intravenous infusion of 0.33-mg/kg cocaine delivered over a 3–9-s period, depending upon the body weight of the animal. Licks on the inactive spout had no effect and the location of the active and inactive spout was counterbalanced across rats and across sessions (days). Drug delivery was signaled by offset of the stimulus cue light, retraction of the spout and onset of the tone and the house light. The tone remained on for a total of 20 s, during which time further responses were not reinforced. The access period to the drug (session) lasted for 1 h. Supplemental water was provided for 2 h a day (45 min after being returned to the home cage) over the first 7 days of acquisition. Due to a slight illness (Sialodacryoadenitis virus), which lasted from sessions 4 to 7, however, all rats were returned to food and water ad libitum on the evening of the seventh session and remained on this schedule thereafter. There was one session daily for 15 days. Dependent measures included the number of contacts made on the active and inactive spouts, the number of infusions delivered and the inter-infusion intervals.

2.5.2. Progressive ratio (PR)

On the 2 days following acquisition, all rats were tested on a PR schedule whereby the contingency was incremented by 10 licks after each infusion. Break point was identified as the last ratio requirement for which the animal received an infusion. The session ended when the rat failed to earn an infusion over a 30-min period or after 4.5 h, which ever came first.

2.5.3. Dose response

The next test examined whether the rats would adjust their responding as the concentration of cocaine (dose) increased and then decreased. The order of dose delivery was the following: 0.66, 1.32, 0.66, 0.33, 0.16, 0.08 and 0.04 mg/kg. Each animal was tested at each dose for an hour a day for 1–3 days in succession. The decision to test for 1, 2 or 3 days was based on the observation of the magnitude of the effect and on our concern about catheter patency. As a consequence, we began testing the 0.66-mg/kg dose for 3 days, then switched to 2 days for the 1.32-mg/kg dose and then to 1 day of testing beginning with the 0.33-mg/kg dose.

2.5.4. Sucrose reinforcement

After all cocaine self-administration testing was completed, we measured the number of licks emitted for a 0.1 M sucrose solution in the testing chamber over a 20-min access period. This task was included to verify that the low level of responding for cocaine by the iron-deficient rats did not reflect a general inability to respond (i.e., a motor deficit).

2.6. Data analysis

All data were evaluated using a mixed factorial analysis of variance (ANOVA) for one between-subjects factor (diet) for variables measured at one time point (e.g., PR, sucrose) or mixed between-subjects factor (diet) and one within-subjects factor (sessions/days or dose). Hemoglobin concentrations were subjected to Student's *t* tests. Post-hoc tests were conducted, when appropriate, using the Newman–Keuls multiple range method with α set at .05.

3. Results

3.1. General health and hemoglobin

Fig. 1 illustrates growth curves and food/water intake for control and iron-deficient animals. It can be seen in the left panel that beginning on Day 28, the iron-deficient animals' growth trajectory departed significantly from that of the controls [$F(31,434 = 102.4$, $P < .0001$]. The right panel shows that food, but not water consumption, was also significantly reduced in the iron-deficient animals [$F(1,14) = 22.7$, $P < .0002$; $F(1,14) = 2.34$, $P < .15$ for food and water, respectively]. When measured at 67 days of age (4 days before acquisition began), hemoglobin values were found to be dramatically and significantly reduced, $t = 15.49$, $P < .0001$, in the iron-deficient animals (4.73 ± 0.21 mg/dl) compared to the controls (14.38 ± 0.55 mg/dl). A similar pattern was revealed (iron-deficient mean $= 5.17 \pm 0.20$; control mean $= 12.48 \pm 1.89$) when reevaluated at 105 days of age at the end of testing, $t = 3.07$, $P < .015$. The 4–5 mg/dl values are consistent with severe iron deficiency. Finally, as discussed in the methods section, all rats demonstrated symptoms of Sialodacryoadenitis virus during acquisition sessions 4–7. This condition is not life threatening, but generally is associated with a reduction in both food and water intake during this time period. As a consequence, all rats were returned to water ad libitum beginning on the evening of the seventh session and remained on this schedule thereafter.

3.2. Cocaine self-administration

3.2.1. Acquisition

All rats, except for one, administered cocaine during the first acquisition session. The one animal that failed to self-administer the drug during the first session, administered cocaine during the second session. As shown in Fig. 2, the iron-deficient rats acquired cocaine self-administration behavior more slowly than did the controls. There was a significant Diet × Sessions interaction [$F(14,168) = 2.4$, $P < .004$]. Post-hoc Newman–Keuls tests of this interaction showed that the iron deplete rats made significantly fewer cocaine infusions per hour than did the iron adequate rats on sessions 8–10, $P < .05$. Thereafter, response rates did not differ. Although it is possible that the illness contributed to the somewhat erratic acquisition function in the control

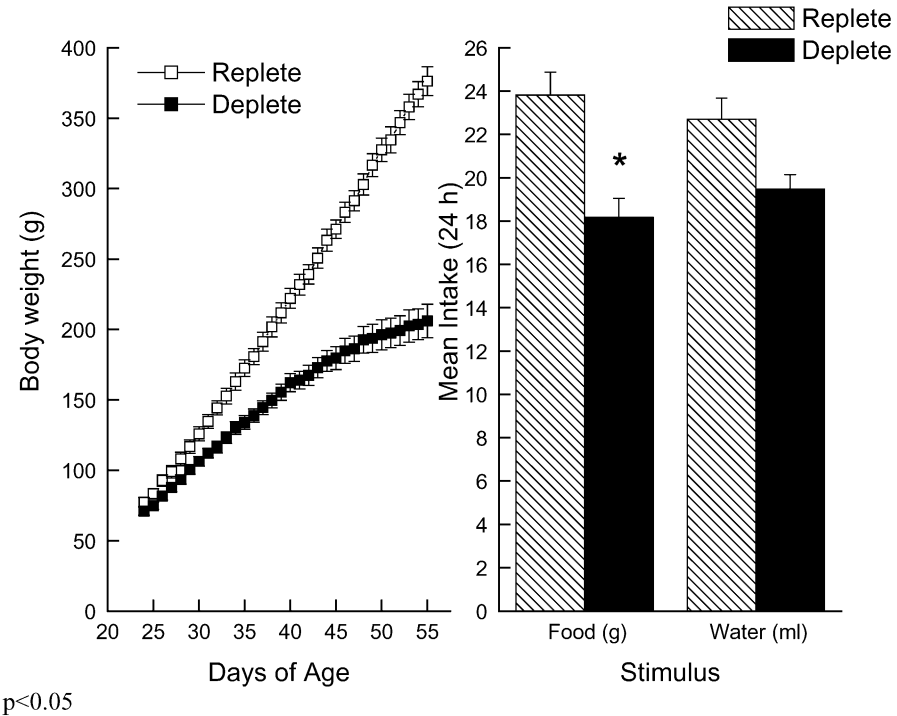

Fig. 1. Effect of iron-deficient diet (vs. control) on body weight (left panel) and food and water consumption (right panel). Male Sprague–Dawley rats were fed an iron-deficient (3.5 ppm) or iron adequate powdered diet (35 ppm) beginning at 21 days of age. Data presented are means and standard errors of the mean.

subjects, it is not likely that it accounts for the retarded acquisition function generated by the iron deplete rats. Specifically, the iron-deficient rats exhibited fewer infusions/h than the controls from the start and this effect was statistically significant on the last day of testing prior to the onset of illness, $t = 4.98$, $P < .04$. During the first session, responses on the inactive spout were nearly equal between the iron-deficient and control animals. In the iron-deficient animals, however, closer examination revealed a significant difference between responses on the active and inactive spout [$F(1,5) = 6.58$, $P < .05$] with fewer responses made on the active than inactive spout. On the last session (session 15), both groups of animals showed significantly more responses on the active than the inactive spout [$F(1,11) = 8.16$, $P < .02$].

3.2.2. PR testing

The data obtained across the two PR sessions were averaged for each animal and analyzed as described above. The extreme right panel of Fig. 2 illustrates that when the animals were subjected to a PR schedule of reinforcement, the control animals maintained a consistent number of infusions as under the FR_{10}, but the response rate of the iron-deficient animals fell off dramatically [$F(1,12) = 4.8$, $P < .05$]. The mean break point for the controls was FR_{200}, three times that found in the iron-deficient animals (FR_{60}).

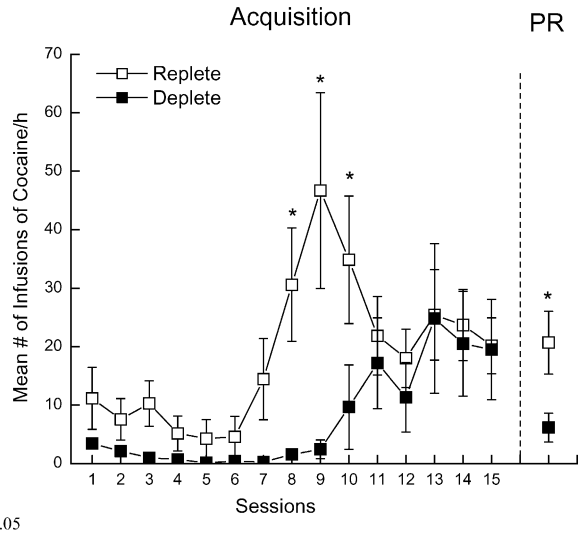

Fig. 2. The effect of iron deficiency on intravenous cocaine self-administration in male, Sprague–Dawley rats. Beginning at 60–62 days of age, the animals were trained to lick an empty water spout for an intravenous injection of cocaine (0.33 mg/kg/infusion). Acquisition was under a fixed-ratio 10 (FR_{10}) schedule of reinforcement. Training consisted of one 1-h session per day for 15 consecutive days. On the day following acquisition, the animals were tested for progressive-ratio responding at the same dose of cocaine. The first infusion thus required 10 licks, the second and additional 10 and so forth. The right panel presents the number of infusions for the control and iron deficient animals. Break point for the control animals was approximately 180 responses, whereas for the iron deficient animals the break point was approximately 60. Data presented are means and standard errors of the mean.

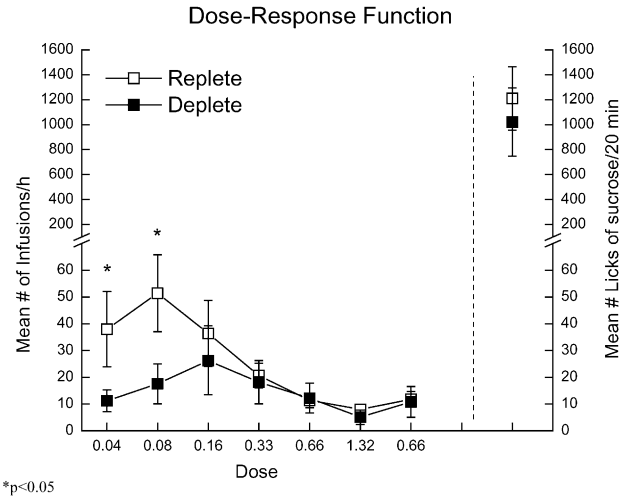

Fig. 3. Cocaine self-administration at varying doses of cocaine (left panel) and operant responding for saccharine reinforcement (right panel). Following testing for response under progressive ratio, the animals were tested for responding at different doses as indicated on the abscissa. Testing was conducted for 1 h on 3 consecutive days at each of the doses. On the day following dose–response testing, the animals were tested for licking for sucrose (0.1 M) reward during a 20-min exposure. Data presented are means and standard errors of the mean.

In other words, the controls made at least 2100 licks during the 4.5-h session; however, the iron-deficient rats made 210 licks in the same amount of time.

3.2.3. Dose response testing

The data collected for each dose of the drug were collapsed across sessions and analyzed as described above. Fig. 3 illustrates the effect of adjusting the dose of cocaine across sessions. A mixed factorial ANOVA revealed a significant Diet × Dose interaction [$F(6,66) = 3.09$, $P < .009$]. Post-hoc Newman–Keuls tests of this two-way interaction showed that iron adequate, but not iron deplete rats, significantly increased responding as the dose of the drug was reduced from 0.16 to 0.08 mg/kg and, again, as the dose was reduced from 0.08 to 0.04 mg/kg, $P < .05$.

3.2.4. Sucrose testing

The possibility must be considered that the failure to respond by the iron-deficient rats reflects a motor, rather than a motivational, deficit. Perhaps, the iron-deficient rats simply cannot generate 2000 licks in a 4.5-h period. Support for this hypothesis, however, was not provided. As shown in the extreme right panel of Fig. 3, the iron-deficient rats, like the controls, made approximately 1000 licks in only a 20-min test period.

4. Discussion

The results from this experiment showed that at the beginning, iron-deficient animals acquired intravenous

cocaine self-administration more slowly than did the controls but, after 15 sessions, the response rates for cocaine for the two groups were essentially identical. When subjected to a PR schedule of reinforcement, the iron-deficient animals stopped responding at FR_{60} whereas the controls persisted responding to FR_{200}. When the dose of cocaine per injection was decreased, the control animals showed a compensatory, increase in responding, whereas the iron-deficient animals did not. Finally, the iron-deficient animals were capable of performing the operant task (i.e., licking) because these rats emitted the same number of licks for sucrose as did the controls.

What are some possible explanations for our observations? One such explanation is that iron deficiency, by virtue of compromising mesolimbic and nigrostriatal dopamine systems reduces cocaine's reinforcing effect. Support for this hypothesis might be garnered by the observations of the retarded acquisition of cocaine self-administration and that the iron-deficient animals failed to compensate for lower doses by increased responding. An alternative explanation is offered by the work of Salamone et al. (2001). According to these authors, interference with dopamine neurotransmission in the nucleus accumbens may not affect rewarding effects of food or perhaps drugs per se. Rather, the effects are seen primarily when an increased work demand (by way of an increased response to reward ratio) is imposed. In fact, we began the acquisition sessions with a response requirement of 10 licks per infusion of cocaine. Thus, it is possible that the iron-deficient rats' apparent reduced motivation for cocaine during acquisition, PR testing and even dose response may be more precisely explained in terms of the amount of effort required to obtain the reward. It should be noted, however, that rats make approximately seven licks per second (Corbit and Luschei, 1969), suggesting that this operant generally requires a minimum of "work" for a rat. Another explanation for the differences might be in terms of impaired associative learning ability in the iron-deficient animals. The distribution of responses between the active and inactive spouts tends to argue against this. In fact, on the very first session, the iron-deficient animals clearly discriminated between the two, making significantly fewer responses on the active than on the inactive spout. By the terminal acquisition session, the pattern reversed in iron-deficient rats who, like the controls, made significantly higher responses on the active than the inactive spout.

In this work, the focus was primarily on the pharmacodynamic rather than the pharmacokinetic aspects of drug self-administration. One possible factor, which should be considered in future studies, is whether iron deficiency alters cocaine distribution and clearance. Indeed, if iron deficiency could slow the rate of cocaine disposition (normally quite rapid with a $t_{1/2}$ of less than 30 min), this could partially explain the lower frequency of self-administration.

Another major issue is whether the effect of iron deficiency is specific to cocaine. Both groups responded equally for sucrose reward; however, this finding demonstrated only that the iron-deficient animals were not impaired in the ability to make the motor response. In our next work, we shall apply the same protocols of fixed-ratio, PR and dose (concentration) response for sucrose to compare to cocaine to try to separate the issue of motivation versus effort required.

Our observations of iron deficiency-related alterations in cocaine self-administration are consistent with our earlier findings showing that iron deficiency dramatically decreased sensitivity to the locomotor effects of cocaine (Erikson et al., 2000), which in turn is consistent with impaired expression and/or functioning of dopamine receptors and the transporter (Erikson et al., 2000, 2001). Previous work by others (Pettit et al., 1984; Caine and Koob, 1994) showed that destruction of mesolimbic dopamine pathways by 6-OH dopamine in rats abolished cocaine self-administration whereas administration of dopamine D_1 and D_2 receptor antagonists (Koob et al., 1987; Caine et al., 1995; Epping-Jordan et al., 1998) or a D_2 partial agonist (Pulvirenti et al., 1998) shifted the dose response curve to the right, i.e., led to an increase in responding for higher doses of cocaine. That is to say, by impairing mesolimbic dopamine pathways, these researchers demonstrated a *decrease* in the reinforcing capability of cocaine that the animals were able to overcome merely by increasing the dose. The mixed D_1 and D_2 receptor antagonist, α-flupenthixol, also caused a right-shifted dose response curve for cocaine self-administration, however, at a high dose, the animals ceased self-administration of cocaine altogether (Ettenberg et al., 1982).

In our initial reasoning about this experiment, we thought that iron deficiency, by impairing but not destroying mesolimbic (and striatal) dopamine function, might produce the same effects as those observed by Koob et al. (1987) when animals were treated with dopaminergic agents but not the neurotoxin or very high doses of the antagonist. Thus, we reasoned that the dose response curve for iron-deficient animals might be right-shifted, compared to the dose response curve generated by controls. In fact, this was not what we found. Instead, we showed a diminished reinforcing effect of cocaine but no accompanying compensatory behaviors in the iron-deficient animals as might be predicted by the earlier pharmacological applications.

There are a number of possible reasons for our findings. First, it is possible that our dietary treatments were too severe and mimicked the 6-OH dopamine or high dose antagonist treatments. In fact, the hemoglobin measures (ca. 4–5 mg/dl) revealed that the animals were indeed severely iron-deficient, with the possible effect to incapacitate the mesolimbic and nigrostriatal dopamine systems beyond what might be observed with the lower doses of the antagonists. Others have shown dopamine-related behavioral deficits even in iron-deficient rats with hemoglobin values of 7–9 mg/dl (Kwik-Uribe et al., 2000). This would be an obvious target value for the next experiment. A second possibility is that the investigators who challenged cocaine self-administration with other agents did not test

naïve animals during challenge, i.e., the animals had been trained to self-administer cocaine prior to the challenge. Our iron-deficient animals were drug-naïve at the start of testing. A final possibility for consideration is that the brief illness at the onset of training may have influenced the outcome. As discussed, this seems unlikely because the iron-deficient rats self-administered less cocaine than did the iron adequate rats even before the onset of the brief period of illness. Moreover, the fact that we observed such dramatic differences between the control and iron-deficient animals once this short-term illness had subsided, provides robust evidence that iron deficiency diminishes the reinforcing effect of cocaine.

We began this study with the idea that iron deficiency early in life might cause animals to administer larger doses of cocaine (hence, reflecting a diminished reinforcing effect of cocaine) and thus constitute a model for early iron deficiency to increase the risk for later cocaine abuse in adolescents. Our results do demonstrate possible altered reinforcing effect of cocaine, but no support for an increased liability for the latter. Of course, a less severe iron deficiency treatment may support this hypothesis, as might the onset of iron deficiency in an already addicted (or drug experienced) rat. These hypotheses remain to be tested. What our results do show, however, is that iron deficiency begun at weaning profoundly decreases, but does not eliminate entirely, the self administration of cocaine in rats. Finally, the question is raised about whether iron-deficiency alters hedonic-like behaviors related solely to dopamine or whether other kinds of pleasure seeking behaviors (e.g., sex, heroin self-administration) may be so affected.

To our knowledge, this is the first report showing that deficiency of a micronutrient can dramatically affect self-administration of a drug that would otherwise be taken readily. In fact, this line of research opens an avenue of inquiry, i.e., the effects of iron (and other micronutrient) deficiency on neuropharmacology in general. There are numerous drugs given to children and adults to either enhance or diminish the effects of dopamine and drugs prescribed to enhance the effects of serotonin and norepinephrine. One question raised is what might be the effect of iron deficiency on the efficacy of methylphenidate in children or haloperidol in adults? Is it possible that the effects of neuropharmacological agents may be diminished, or worse, toxicity enhanced?

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