Lesions of the amygdala central nucleus interfere with blockade of satiation for peanut oil by Na-2-mercaptoacetate

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Previous research suggests that the amygdala central nucleus (CN) is an important neuroanatomical substrate for energy balance, and the detection of lipoprivic state signals in particular. We recently demonstrated that rats with selective lesions of the CN did not show enhanced conditioned responding toward oil-predicting stimuli after administration of the lipoprivic agent, Na-2-mercaptoacetate (MA; Benoit, Morell, & Davidson, 1999). In the present experiment, rats with lesions of the CN were trained in such a way that a stimulus predicted the delivery of either sucrose pellets or peanut oil under food deprivation. They were then given access to the foods under food satiation after an injection of either saline or MA. Finally, rats received a behavioral test for learned satiation responses to the stimulus (i.e., reduced responding) in the absence of food or MA. Results showed that MA blocked acquisition of satiation responses in rats trained with peanut oil, but not sucrose. Rats with lesions of the CN, however, acquired satiation responses equally, regardless of macronutrient or treatment. These data extend previous findings suggesting that the CN is a critical brain structure for rats' ability to detect lipoprivation and introduce an additional behavioral paradigm for the study of macronutrient selection.

Discussions of the control of food intake regulation usually include the idea that departures from energy homeostasis provide a stimulus for feeding, and for behavior that is instrumental to obtaining food. A related proposition, although one that is not as widely accepted, is that intake of specific macronutrients (e.g., fats, carbohydrates) is also regulated by homeostatic mechanisms. For example, Bray (1994) suggested that the intake of fats, carbohydrates, and proteins is "regulated separately and then integrated into total energy needs" (p. 19). According to Bray, different stores exist for each of these metabolic fuels, and feedback specific to each store signals departures from macronutrient homeostasis.

Evidence that animals can be simultaneously satiated for one macronutrient (e.g., carbohydrate), but not satiated for another (e.g., fat), would be fundamental in making the case that bodily supplies of different macronutrients are regulated independently. One approach to obtaining this type of evidence has been to measure intake as a consequence of restricting availability of one, but not another, type of macronutrient in the diet. If animals respond to this manipulation by selectively increasing their intake of the restricted macronutrient when that macronutrient is

made available, this would be consistent with the hypothesis of independent regulation.

Unfortunately, animals will often differ in their macronutrient preferences, even under conditions of apparent total metabolic repletion (e.g., Galef, 1991). Therefore, it is possible that in any given experiment, taste preference for one macronutrient could mask or greatly reduce the effects of dietary restriction of another macronutrient. In addition, it seems clear that for fat and carbohydrate, departures from homeostasis could activate physiological mechanisms that are capable of restoring macronutrient balance. Although the costs in terms of efficiency of energy utilization are high (e.g., Bray, 1994), animals can convert stored fat into circulating carbohydrate and can convert circulating carbohydrate into stored fat. The operation of this type of mechanism could serve to weaken or even abolish the specific deficit signals that might be involved with the behavioral regulation of macronutrient intake.

One purpose of the present research is to study, under conditions in which the influence of taste preferences and compensatory physiological mechanism is reduced or eliminated, whether or not animals can be selectively satiated for one macronutrient and not satiated for another. To achieve this objective, we employed a research design similar to that developed by Balleine and Dickinson (see Dickinson & Balleine, 1994, for a review). These investigators trained hungry rats to press a lever to obtain food pellets. After asymptotic performance was achieved, the rats were given the opportunity to eat the pellets from a dish that was located outside of the chamber where lever-press training occurred. Some rats received the pellets

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when hungry, while others ate the pellets when food sated. The rats were subsequently returned to the original training apparatus, where the effects of food satiation on the performance of leverpressing was tested in extinction (i.e., no pellets were delivered). During extinction testing, satiation suppressed barpress performance only for rats that had previously consumed the food pellets when satiated.

These findings indicated that satiation has little capacity to reduce the performance of appetitive responses until the animal has experienced the consequences of eating food when satiated.¹ We use this empirical relationship as an analytical tool to examine whether or not selective antagonism of fat metabolism, induced by acute systemic administration of Na-2-mercaptoacetate (MA), could interfere selectively with satiation for fat relative to carbohydrate. The acute use of MA rather than longer term dietary restriction to induce lipoprivation was intended to minimize interference from compensatory physiological mechanisms that might normally block the production or reduce the intensity of lipoprivic cues. In addition, neither food nor eating occurred when the effects of MA were measured. Thus, it is difficult to see how differential taste preferences could influence those effects.

A second goal of this experiment was to assess further the potential role of the amygdala central nucleus (CN) in the regulation of macronutrient intake. The results of previous studies (e.g., Benoit, Morell, & Davidson, 1999; Ritter & Hutton, 1995) indicate that animals with selective ibotenate lesions of the amygdala CN showed reduced behavioral sensitivity to lipoprivation produced by administration of MA. It may be that CN lesions interfere with the detection of lipoprivic signals that are transmitted to the brain via neural or humoral pathways. It is also possible that an intact CN is needed for the detection of lipoprivic signals to be expressed as appetitive or consummatory behavior. In either case, damage to the CN would be expected to interfere with effects of lipoprivation induced by administration of MA.

The design of this experiment is depicted in Table 1. Hungry rats were first given training in a conditioning

chamber in which an auditory stimulus (a 10-sec tone) that signaled the delivery of an unconditioned stimulus (US). For half the rats, the US was peanut oil (100% fat) while the US was sucrose pellets (100% carbohydrate) for the remaining rats. At the completion of this training phase, rats were given free access to conventional lab chow in the home cage. Next, half the rats from each US group (sucrose and oil) received selective ibotenate lesions of the amygdala CN. The remaining rats were assigned to be either sham-lesioned or nonlesioned controls. Following recovery from surgery, all the rats were food sated and were placed in an opaque white tub (Context B), where they were allowed to eat the same food they had received during training. About 1 h before the beginning of this satiated exposure phase, MA (400 μ mol/kg, i.p.) was administered to half the rats given peanut oil and sucrose, respectively, in the CN-lesioned and control groups. The remaining rats received an equal volume of isotonic saline, i.p. Finally, all rats were returned to the original training apparatus, where the capacity of the originally trained auditory cue to evoke appetitive behavior was measured. All rats remained food sated and no peanut oil or sucrose pellets were delivered during this test phase (i.e., the test was conducted during extinction).

Administration of saline should not interfere with the experience of satiation. Therefore, saline controls would have been food sated when they consumed either peanut oil or sucrose pellets during the exposure phase. According to Dickinson and Balleine (1994) and Davidson (1998), this experience of eating while food sated would enable satiation to suppress appetitive responding to either the cue for oil or the cue for sucrose during the test phase. Unlike saline, administration of MA was expected to interfere with the experience of satiation. If that interference occurred in a nonspecific way, then the rats would be satiated for oil and sucrose, respectively, during the exposure phase. Consequently, in the absence of this experience, satiation would have little capacity to suppress appetitive responding to either the oil or the sucrose cue during testing. Of most interest is the possibility that MA might interfere selectively with the experience of satiation for fat but not for carbohydrate. If this were to occur, MA administration might block satiation for rats trained with and given exposure to oil, but not for rats trained with and exposed to sucrose. Evidence for this effect would take the form of greater test phase suppression of responding to the cue for sucrose than to the cue for oil for rats treated previously with MA. Finally, to the extent that effects of treatment with MA are mediated by the amygdala CN, damage to that site should disrupt or abolish any nonspecific or selective effects of MA that are revealed during subsequent testing.

METHOD

Subjects

Subjects were 56 naive male Sprague-Dawley albino rats (Harlan Sprague Dawley, Inc., Indianapolis, IN). Upon arrival, rats were approximately 90 days old and weighed 275–300 g. Subjects were

Table 1
Exposure to Peanut Oil and Sucrose Pellets Under Satiation and Lipoprivation in Control and in CN-Lesioned Rats

Groups	Context A Training Deprivation	Surgery Ad-Lib Food	Context B Exposure Satiation	Context A Test Satiation
Control-Oil-MA	CS-Oil	—	Oil (MA)	CS
Control-Oil-Sal			Oil (Sal)	
Control-Suc-MA	CS-Suc		Suc (MA)	
Control-Suc-Sal			Suc (Sal)	
CN-Oil-MA	CS-Oil	IBO CN	Oil (MA)	CS
CN-Oil-Sal			Oil (Sal)	
CN-Suc-MA	CS-Suc		Suc (MA)	
CN-Suc-Sal			Suc (Sal)	

Note—CS = tone; Context A = training chamber; Context B = exposure tub, 25-min sessions, trials per session. Total eight sessions; two exposure sessions (15 min) with 30 USs per session. Sal, saline; MA, Na-2-mercaptoacetate; Suc, sucrose; CS, conditioned stimulus; CN, central nucleus; IBO, ibotenic acid.

housed individually in stainless steel cages and maintained on a 12:12-h light:dark cycle with lights on at 0700 h. The rats were maintained on Purina rat chow. Water was available ad lib in the home cage throughout the experiment, except during experimental sessions. All rats were weighed prior to each experimental session. Prior to the beginning of training, food rationing was used to gradually reduce all rats to 85% of free-feeding bodyweight. During training, food rations were given 15 min after the completion of daily sessions. All experimental sessions began at 1600 h.

Apparatus

All conditioning and testing procedures were conducted in four identical conditioning chambers (Context A) constructed of aluminum end walls and clear Plexiglas sides, measuring $21.6 \times 21.6 \times 27.9$ cm (animals were run in training and test sessions in squads of 4 animals). The floor of each chamber consisted of stainless steel bars, .48 cm in diameter, spaced 1.9 cm apart. A foodcup was located in one end wall of each chamber. Each chamber was seated within a larger, closing sound-attenuating chamber. These boxes served as training and test contexts. During training, the chambers were darkened and ambient noise was kept minimal. Exposure sessions were conducted in eight identical plastic carrying tubs measuring $47.5 \times 27 \times 19.5$ cm with stainless steel grid covers (Context B). In this phase of the experiment, the CS was produced by a 1000-Hz tone located outside the foodcup wall of each chamber. During Phase 2 exposure sessions, ambient light in the experimental room was kept maximal. Peanut oil and sucrose pellets were delivered in small glass dishes.

Data collection. Changes in appetitive behavior were monitored by a computer-controlled infrared monitoring system. Sixteen electronic beams (ENV-256C Infra-red Photobeam Controller & DIC-712 Photobeam Inputs, Med Associates, Inc.) lined each cage from side wall to side wall approximately 2 cm above the grid floor. These beams were controlled and data analyzed by software developed in the lab for measurement of behavioral activity and appetitive behavior. The computer was programmed to record the location of each animal during each 10-sec trial as well as the 10 sec before each trial began. Appetitive behavior was determined by dividing the number of times an animal interrupted the photobeam immediately adjacent to the foodcup by the total number of observations during each session (see Davidson, Altizer, Benoit, Walls, & Powley, 1997, for details). The computer and relay panel operating the photobeams were located in an adjoining room.

Pharmaceuticals. Sodium chloride (NaCl) and MA (Sigma Chemicals, Inc.) were prepared in isotonic solutions and delivered according to procedures described by Benoit and Davidson (1996). MA 400 μ mol/kg and saline were administered in 2-ml/kg i.p. injections.

Procedure

Each training session included 15 deliveries of a 10-sec tone CS immediately followed by delivery of a US at an intertrial interval (ITI) of 120 sec. For half the animals, the US was one 45-mg Noyes sucrose pellet. The other half received 1 drop of Planter's peanut oil (.15 ml) as the US. Data were recorded by computer during the 10-sec CS as well as the 10 sec immediately preceding the CS delivery. After the completion of each training session, rats were returned to their home cages and received a daily ration of food pellets (approximately 15–20 g) 15 min later. Pavlovian training continued for eight sessions.

Exposure. After training was completed, all rats were given ad-lib access to lab chow for the remainder of the experiment. Half the rats that had been trained with oil and half that had been trained with sucrose were assigned to receive ibotenate lesions of amygdala CN. Half the remaining rats trained with each US were assigned to a sham-lesioned control group and half were unoperated

controls. Rats were assigned to surgery groups by matching on performance at the end of training. Exposure sessions began after allowing 2 weeks for animals to recover from surgery. Before each of the two 15-min exposure sessions, the rats were weighed and food was removed from the home cage. They were then injected with MA or isotonic saline and returned to the home cage for 1 h. During each session, ambient light (from overhead fluorescent lamps) was increased and noise was reduced. Rats received either 30 sucrose pellets or 30 drops of peanut oil during each of exposure sessions. During exposure, sucrose and oil were placed in glass dishes inside the plastic tubs before the rats were placed in the tubs.

Testing. Two days following the last exposure session, rats were returned to the original training context for one 30-min tone extinction test. The tone was delivered as described for training (15 trials, ITI 2 min), except that no oil or sucrose was delivered. Appetitive behavior was measured during the CS and the 10 sec immediately preceding the CS. All rats remained on ad-lib feeding until immediately before the test session.

Surgical and Anatomical Procedures

Thirty-two rats received ibotenate lesions of the CN. These subjects were anesthetized by i.p. injection of sodium pentobarbital. The rats were placed in a stereotaxic instrument, and the bone overlying the CN was removed. Lesions were made with bilateral injections of .08 ml of ibotenic acid (IBO) at a concentration of 10 mg/ml, through a fine glass micropipette at -2.0 AP, ± 3.8 , -7.2 DV, and ± 4.1 , 7.2 DV (see Jarrard, 1989, for details). The remaining rats ($n = 24$) were controls. Twelve animals were sham operated; the micropipette was placed at each coordinate, but no injection was administered. Consistent with previous reports from our labs, the remaining 12 control animals received only i.p. injections of the anesthetic. After surgery was completed, all rats were placed on ad-lib feeding and allowed 2 weeks for recovery. Only data from rats that had at least 25% bilateral damage to the amygdala CN and minimal extra-CN damage were included in any analysis. Three rats in each condition were excluded from analyses.

RESULTS

Behavioral

Training. Figure 1 shows mean percent appetitive behavior during 15-trial blocks of acquisition. By the end of acquisition, all rats showed more appetitive behavior during the CS than the pre-CS period. Animals that received sucrose as the US showed more appetitive behavior during the tone CS than did animals that received peanut oil.

A mixed $2 \times 2 \times 3$ analysis of variance (ANOVA) using period (pre-CS vs. CS), US (oil vs. sucrose), and session (6–8) was conducted on mean amount appetitive responding from the final three sessions of acquisition. This analysis yielded a main effect of period [$F(1,22) = 227.78, p < .01$] and a main effect of US-group [$F(1,22) = 10.90, p < .01$]. An additional ANOVA, including surgery-dummy and drug-dummy as factors, was conducted on data from the final session of training. This analysis yielded neither a main effect of either dummy variable nor an interaction with either dummy variable and any other factor. This outcome indicated that there were no significant differences in terminal training performance between groups that were assigned to receive different posttraining treatments.

Figure 1. Mean percent appetitive behavior across eight sessions of 15 trials each. Filled symbols represent data for conditioned stimulus (CS) periods; open circles represent data for pre-CS periods. Circles represent rats in Group Sucrose while triangles show data for rats in Group Oil.

Exposure. Two animals failed to consume all of the oil during the first exposure session on the 1st test day. These 2 animals were given an additional exposure session to peanut oil. One animal received exposure after injection of MA, and one received exposure after injection of saline. All of the remaining rats consumed all of the oil or sucrose that was available during the first two exposure sessions.

Testing. Figure 2 shows mean percent appetitive CS-period responding collapsed across all extinction trials. Amount of test responding appeared to have been dependent on the type of US, type of exposure, and lesion. For control animals, amounts of appetitive behavior evoked by the cue for sucrose did not differ on the basis of the exposure phase treatment (i.e., saline vs. MA). Further, the pattern of appetitive behavior was the same for control and lesioned animals. In contrast, control animals that had been injected with MA prior to the exposure phase showed more appetitive responding to the cue for oil than did controls that had been injected with saline. As shown in Figure 2, rats with IBO lesions of the CN exhibited similar amounts of appetitive behavior to sucrose and to oil cues regardless of whether they received MA or saline during the exposure sessions.

The statistical significance of these observations was assessed with 2×2 between-subjects ANOVAs using

surgery (control vs. lesion) and exposure (MA vs. saline) as factors on CS-period appetitive behavior collapsed across all test trials. Comparison of these factors on appetitive responding to only the cue for sucrose revealed neither a main effect of surgery nor a main effect of exposure (largest $F = 2.16$, $ps > .05$). On trials with the oil cue, the ANOVA revealed a significant surgery $\times$ exposure interaction [$F(1,17) = 4.72$, $p < .05$]. No reliable main effects were found (largest $F = 1.19$).

For control rats, Newman-Keuls post hoc tests revealed that appetitive behavior on oil cue trials was significantly greater if the rats had been treated with MA than if they had been treated with saline during the exposure phase. Responding on oil cue trials for rats treated previously with MA was also significantly greater for controls than for rats with CN lesions ($ps < .05$). Finally, responding on oil cue trials was not dependent on exposure manipulation (MA vs. saline; $ps > .05$) for rats with lesions of the CN.

Anatomical

Consistent with some previous reports (e.g., Holland & Gallagher, 1993a, 1993b), the criterion for including a CN-lesioned rat in the statistical analysis was at least 25% bilateral damage of the amygdala CN (i.e., no more than 75% of visible control CN), with minimal unilateral

Figure 2. Mean percent appetitive behavior during test session. The left panel shows data for Group Sucrose while the right panel shows data for Group Oil. Left pairs of bars show data for rats with lesions of the amygdala central nucleus (CN) while right pairs of bars show data for controls (Con). MA, Na-2-mercaptoacetate; SAL, saline.

damage to surrounding structures. To assess damage to the CN, sections with discernible CN cells were traced by computer-aided video tracing software (Bioquant). The CN visual extent (based on Paxinos & Watson, 1986) of 2 control animals was used as a baseline for determining average area of the CN through 18 sections, bilaterally. In all but 2 animals, there was at least 45% bilateral damage to CN cells. In addition, 5 rats were dropped because of an error in histological preparation. Of the rats with verified acceptable lesions, 5 were trained with oil and 5 were trained with sucrose prior to treatment with MA during the exposure phase, while 4 were trained with oil and 6 were trained with sucrose prior to treatment with saline during exposure.

DISCUSSION

According to recent accounts (Balleine & Dickinson, 1991, 1992; Davidson, 1998; Dickinson & Balleine, 1994), animals must learn that the consequences (e.g., postingestive aftereffects) of eating a given food are different when that food is consumed under food satiation as opposed to when it is consumed under hunger. This learning occurs when a food, consumed previously only when the animal was hungry, is eaten subsequently when the animal is food sated. Until an animal learns this relationship, satiation will be largely unable to suppress appetitive behavior evoked by cues that are associated with the delivery of that food.

The design of the experiment reported here was based on the idea that if supplies of fats and carbohydrates are

regulated separately at homeostatic levels, animals might learn this empirical relationship separately for each of these macronutrients. We tested this idea by examining the effects of pharmacological lipoprivation induced by injection of MA on what rats learned about the consequences of eating sucrose (100% carbohydrate) and peanut oil (100% fat) when they were food sated. The capacity of satiation to suppress responding to a tone that had been established previously as a cue for sucrose or a cue for oil was then assessed. One apparent interpretive difficulty with the present experiment is that no rats received exposure to sucrose while food deprived. Thus, it would seem difficult to rule out the possibility here that sucrose may not be susceptible to incentive learning manipulations in the same way as peanut oil. However, we rely on previously collected data that suggest this is not the case. Previous work from other labs as well as our own experiments has demonstrated the basic incentive learning finding using a variety of USs, including sugars (see Davidson, Morell, & Benoit, 2000; Dickinson & Balleine, 1994, for reviews).

The results of this experiment provided clear evidence that lipoprivation induced by MA interfered with learning about the consequences of eating oil when food sated but did not interfere with learning about the consequences of eating sucrose. Administering MA prior to giving otherwise food-sated rats the opportunity to eat sucrose pellets had effects on subsequent test phase performance that were no different from those after administration of saline. That is, food satiation was equally effective at suppressing the capacity of a cue for sucrose to evoke appeti-

tive responding during testing, independent of whether MA or saline had been administered when sucrose had been consumed under satiation during the exposure phase. Apparently, rats given MA when food sated learned about consequences of eating sucrose under satiation. In contrast, MA interfered with learning about the impact of satiation on the aftereffects of eating oil when satiated. This pattern of results is consistent with the view that MA prevented the rats from being satiated for fat, but did not prevent them from being satiated for carbohydrate. More generally, these results support the hypothesis that rats can be satiated for one macronutrient without being satiated for another. As noted, this capacity would seem to be a requirement for any view that proposes that bodily supplies of different macronutrients are monitored and regulated independently.

CN and lipoprivation. The results of this experiment also showed that the effects of MA were no different from the effects of saline in rats that had sustained selective damage to the CN. However, it should be noted that rats with lesions of the CN appeared to show overall increased appetitive behavior, including sustained appetitive behavior on the oil-predicting CS. While this may be an intriguing result, the presence of overall increased responding does not detract from the finding that saline- and MA-treated rats did not respond differently, which is the purpose of the present experiment. As previously suggested, the CN has been implicated in the detection or utilization of internal signals of lipoprivation. For example, lesions of the CN impair the normal feeding response to lipoprivic (and to a lesser extent glucoprivic) challenges produced by pharmacological antimetabolites (see, e.g., Ritter & Dinh, 1994; Ritter & Hutton, 1995). Further, Horn and Friedman (1998a, 1998b) recently showed that doses of the lipoprivic agent methyl-paloxirate and fructose analog, 2,5-anhydro-D-mannitol (2,5-am), both of which augment food intake in ad-lib fed rats, also increased *c-fos* like immunoreactivity in several hindbrain and forebrain structures, including the CN.

Results from earlier reports (e.g., Ritter & Hutton, 1995) have demonstrated that animals with CN lesions are insensitive to lipoprivation produced by administration of MA. Further, we have previously demonstrated that lesions of the CN prevented lipoprivic-induced enhancement of responding to conditioned stimuli that predict delivery of peanut oil (Benoit et al., 1999). In that experiment, rats were trained so that one CS predicted the delivery of sucrose while another CS predicted the delivery of peanut oil. In control animals, administration of MA enhanced conditioned responding for the oil-associated CS, but not the sucrose-associated CS. Rats with lesions of the CN, on the other hand, were unresponsive to administration of MA. The present results confirm and extend those previous findings by administering behavioral tests well after the effects of MA have subsided. Thus, if previous differences between control and lesioned rats were due to a behavioral impairment,

rather than a deficit in rats' ability to detect lipoprivation, lesioned rats in the present experiment should have responded more like controls.

Summary and perspectives. In summary, these findings extend those of previous studies showing that the CN plays an important role in the regulation of food intake and energy balance and that the CN is a critical structure for animals' ability to detect and utilize peripheral signals of lipid energy deprivation. In addition, results from the present experiment demonstrate use of a Pavlovian conditioning preparation for the study of macronutrient selection. The present results suggest that the current paradigm will be a useful technique for the investigation of specific macronutrient (e.g., fats) deprivation states. One beneficial aspect of the present paradigm is that behavioral tests are conducted when all animals are under the same deprivation state. Much previous work on macronutrient selection has been confounded by modifications in taste, palatability, and other variables caused by selective deprivation manipulations. In addition, because testing is conducted in the absence of food itself, the current paradigm has the ability to overcome preexisting macronutrient preferences, which animals may exhibit in the presence of total metabolic repletion.

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NOTE

1. There are differing ideas about how experience with eating food when satiated influences subsequent behavior. Although we will not attempt to evaluate these alternatives in the present study, a more detailed exposition of these ideas can be found in Dickinson and Balleine (1994) and Davidson (1998).

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