

BRIEF COMMUNICATION

The Effect of High-Fat Diet on Extinction and Renewal

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Diets high in saturated fats are linked to health problems and impairments in cognitive function in humans. Recent evidence suggests that exposure to a high-fat diet can impair rats' ability to appropriately inhibit responding to stimuli that are reinforced in some circumstances but not in others. Here, we examined the effects of exposure to a high-fat diet on the context-specific renewal of extinguished responding. Rats first received pairings of a noise stimulus with a food reinforcer. After 14 days of exclusive access to either a high-fat or a matched control diet, rats received nonreinforced presentations (extinction) of the noise in either the same context in which they were trained or a different context. Finally, responding to the noise was evaluated in the original training context in all rats. In control rats, substantial renewal was observed; that is, responding was greater if extinction was conducted in a context different from that of training and testing. Renewal was significantly less robust in rats fed the high-fat diet despite evidence that they were at least as sensitive to context change as control rats. Implications of these results for models of relapse and treatments for phobias, addiction, and overeating are discussed.

Keywords: high-fat diet, renewal, extinction, context, inhibition

Diets that contain high levels of saturated fat are associated with a range of health problems in humans, including diabetes, obesity, excess abdominal fat (central adiposity), cardiovascular diseases (Eckel & Krauss, 1998; Pi-Sunyer, 1991; Van Itallie, 1979), and a number of cognitive deficits, including those that characterize Alzheimer's disease (Gustafson et al., 2007; Kanaya et al., 2009). It is interesting that some of these cognitive deficits have been associated with abnormalities in the structure and function of the hippocampus (Gustafson, 2008; Gustafson et al., 2007; Kanaya et al., 2009; Pasinetti & Eberstein, 2008; Vanhanen et al., 2006; Whitmer, Gunderson, Barrett-Connor, Quesenberry, & Yaffe, 2005; Yaffe, 2007). Here, we examined the effect of brief exposure to a high-fat diet on rats' performance in a simple Pavlovian conditioning task known to be sensitive to hippocampal dysfunction, the renewal of extinguished responding after contextual change (Ji & Maren, 2005).

Repeated presentations of a conditioned stimulus (CS) in the absence of the unconditioned stimulus (US) with which it had previously been paired result in decreases in the probability or magnitude of the conditioned response (CR). Considerable evidence suggests that this extinction does not reflect simple erasure of the original learning but rather the acquisition of new, inhibitory learning, leaving the subject with two opposing memories,

CS→US and CS→no US (Bouton, 2000). As extinction proceeds, the second, newer memory suppresses activation of the first. However, this suppression appears to be more context-dependent than the original CS→US memory. The original CR often re-emerges if the CS is presented in a spatial, temporal, or internal state context different from that in which extinction occurred ("renewal"; Bouton & Ricker, 1994) or if the extinction context is altered prior to testing by inserting events such as the US into it ("reinstatement"; Bouton & Peck, 1989). Thus, a number of postextinction manipulations appear to release the original CS→US memory from the inhibition acquired in extinction learning.

Evidence from both humans and animals implicates the hippocampus in a number of learning and memory functions that might be involved in these extinction phenomena. For example, the hippocampus plays an important role in spatial learning and building configural representations (Holland & Bouton, 1999). Similarly, a hippocampal-dependent pattern separation process (e.g., Clelland et al., 2009; Yassa & Stark, 2011) might be involved in distinguishing between memories of reinforced and nonreinforced trials. Moreover, the hippocampus has long been implicated in the inhibition of contextually inappropriate memories (e.g., Anderson et al., 2004; Morris, 2006).

Recently, Davidson and colleagues (e.g., Davidson, Kanoski, Schier, Clegg, & Benoit, 2007; Kanoski & Davidson, 2010; Kanoski, Meisel, Mullins, & Davidson, 2007; Kanoski, Zhang, Zheng, & Davidson, 2010) found that performance on tasks known to be dependent on hippocampal function was impaired in rats that had consumed a diet high in saturated fat. In some cases, rats demonstrated deficits in their ability to inhibit the memory of a previously obtained reward after as little as 3 to 10 days' exposure to a high-fat diet. By contrast, that same dietary exposure produced no deficits in performance on task variants thought not to demand

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hippocampal function. Results from those studies suggest that deficits induced by consumption of saturated fat may target tasks that demand selection among competing excitatory and inhibitory memories.

In the present experiment, rats were first given Pavlovian appetitive conditioning in which a noise CS was paired with a food US in a distinctive context. After a period of exposure to a high-fat or control diet, the rats received extinction training of the noise in the same context as acquisition or in a different context. Rats were then returned to their original conditioning context and tested for renewed responding to the CS. If exposure to a high-fat diet impairs acquisition or expression of competing inhibitory memories, those rats might show impairments in extinction. At the same time, if such exposure especially interferes with contextual control of extinction learning, then renewal might be reduced.

Materials and Method

Subjects

The subjects were 32 naïve male Long–Evans rats (Charles River Laboratories, Raleigh, NC), weighing 328–369 g at the start of the experiment. They were housed individually in a temperature-controlled colony illuminated from 7:00 a.m. to 7:00 p.m., with free access to water. The rats were given 1 week to adapt to the colony; each rat was handled for approximately 2 min every other day during this period. Rats were food-deprived and maintained at 85% body weight by limiting access to chow (Harlan Teklad #2018, Madison, WI) for 1 week before the start of training.

Diets

A high-energy diet, high in saturated fat (lard-based) and sucrose (D12451, ResearchDiets, New Brunswick, NJ), was used as the high-fat (HF) diet. This diet was nutritionally adequate, with a caloric density of 4.73 kcal/g (45% kcal from fat), and contained the following (g/kg): 200 g casein, 72.8 g corn starch, 100 g maltodextrin, 172.8 g sucrose, 50 g cellulose, 25 g soybean oil, and 177.5 g lard. A matched control (CTL) diet (D01072401, ResearchDiets) had a caloric density of 3.85 kcal/g (10% kcal from fat), and contained the following (g/kg): 200 g casein, 452.2 g corn starch, 75 g maltodextrin, 172.8 g sucrose, 50 g cellulose, 25 g soybean oil, and 20 g lard.

Apparatus

The behavioral training apparatus consisted of two sets of four individual chambers (22.9 cm × 20.3 cm × 20.3 cm), each with aluminum front and back walls and clear acrylic sides and top. In both sets, a dimly illuminated food cup was recessed in the center of one end wall and an (unused) identical cup was recessed in the center of the opposite end wall. Infrared photocells placed just inside the cups were polled (1 kHz) by computer circuitry. An infrared activity monitor (Coulbourn Instruments, Allentown, PA) was mounted on the ceiling of each chamber. Each chamber was enclosed in a sound-resistant shell. Ventilation fans provided a 70-dB masking noise. Placed above each box was a bank of infrared light-emitting diodes, which provided constant dim illu-

mination, invisible to the rat. A TV camera was mounted within each shell to provide a view of the chamber. The output from each camera was digitized and merged into a single image of all four chambers for display and recording.

Chambers contained distinct contextual cues and were used as two different counterbalanced contexts (Contexts X and Y). For each rat, the context in which initial training occurred was defined as Same (X or Y) and the other context as Different (Y or X, respectively). In the four Context X chambers, a solid metal insert was placed inside the box, covering the floor. This insert also provided a bench (5 cm × 5 cm × 19 cm), concealing the unused food cup. One acrylic side had 3.81-cm-wide horizontal stripes, spaced 3.81 cm apart. The inner surfaces of these boxes were wiped with a 30% solution of distilled white vinegar before each session. In the four Context Y chambers, the floor consisted of 0.48-cm stainless steel rods spaced 1.90 cm apart. One acrylic side had 3.81-cm-wide vertical stripes, spaced 3.81 cm apart. The inner surfaces of these boxes were wiped with a 50% solution of Formula 409 (Clorox Company, Oakland, CA) before each session.

Procedure

Rats were first trained to consume the sucrose pellet reinforcer in two 64-min sessions. In each of these daily sessions, there were 16 deliveries of two 45-mg sucrose pellets (Formula 5TUT, Test Diets, Richmond, IN) used as the reinforcer throughout the study. All rats received one session in Context X and one session in Context Y (counterbalanced).

Next, all rats received training of an auditory cue with the reinforcer in the Same context (X or Y, counterbalanced). In each of eight 64-min daily sessions, the rats received sixteen 10-s reinforced presentations of an 80-dB white noise. The mean inter-trial interval (ITI) was 240 s (range = 120–360 s).

One day after the completion of acquisition training, half of the rats were fed the HF diet and half were fed the CTL diet ad libitum for 7 days. For an additional 7 days, the rats were then food-deprived and maintained at 85% of their new body weights by giving equal-calorie measured access to their respective diets. Rats were kept at these weights for the remainder of the experiment to maintain motivation during extinction training. These weights did not differ significantly across conditions (see Table 1).

Next, the rats received six 64-min sessions of extinction, each including 16 nonreinforced presentations of the noise (mean ITI = 240 s). Half of the rats in each dietary condition received extinction in the same context in which they were trained (HF-Same and CTL-Same) and half received extinction in the different context

Table 1
Group Mean (SEM) Body Weights (g) Before and After Diet Manipulation

Diet	Context	Before	After
HF	Same	296.3 (3.60)	327.7 (6.03)
HF	Different	301.9 (4.05)	338.2 (6.67)
CTL	Same	297.0 (2.36)	323.4 (3.43)
CTL	Different	297.0 (2.69)	327.1 (2.63)
Overall mean (SEM)		297.0 (2.36)	329.1 (2.57)

Note. HF = high-fat diet; CTL = control diet.

(HF-Diff and CTL-Diff). Finally, all rats were returned to the same context and given four daily tests of renewal of extinguished food cup responding. Each 16-min renewal test session included four 10-s nonreinforced presentations of the noise (mean ITI = 240 s).

Response Measures and Data Analysis

The measure of conditioning was the amount of time spent with the rat's head in the food cup during any designated time interval divided by the duration of that interval (% time in food cup). Sampling intervals included the 5-s period immediately prior to noise presentations (pre-CS), the two 5-s intervals of the 10-s CS presentation, and (in extinction and test sessions) the two 5-s periods immediately after CS termination. Because previous studies (e.g., Holland, 1977) showed that food cup behaviors are typically timed to occur near (just before and just after) the time of reinforcer delivery, we focused on responding during the last 5 s of the cue interval in the acquisition phase, and in that interval together with the first 5-s period after CS termination (the "peak interval") in the extinction and test sessions in which food was not presented. To reduce within-group variance due to individual differences in baseline responding, we reported elevation over pre-CS responding as our primary response measure. Pre-CS responding, which we also reported, never differed significantly between conditions.

Elevation scores and pre-CS responding were analyzed with separate analyses of variance (ANOVAs), with context (same or different) and diet (HF or CTL) as between-subjects variables and (if appropriate) session as a repeated measure. All within-subject effects and interactions included a Geisser–Greenhouse correction for nonsphericity.

Results

Acquisition

Responding increased rapidly across sessions in all groups (see Figure 1A) regardless of the identity of the training context (X or

Y). A preliminary analysis found no significant difference in responding in Context X compared with Context Y, $F(7, 168) = 1.69$, $p = .154$, so the context identity variable was dropped from further consideration. A Context \times Diet \times Session ANOVA (based on rats' subsequent assignments to context and diet conditions) showed only a significant effect of session, $F(7, 196) = 75.26$, $p < .001$; other $ps > .357$. Pre-CS responding did not differ among the four groups (range = $6.9 \pm 1.3\%$ to $12.6 \pm 2.9\%$), supporting the use of elevation scores. A comparable ANOVA of pre-CS responding reported no significant main effects or interactions involving context or diet, $ps > .350$, nor was the effect of session significant, $F(7, 196) = 1.49$, $p = .172$.

Diet Exposure

All rats gained weight rapidly when given ad libitum exposure to the diets. Because both diets were highly palatable and of high caloric density, all rats gained comparable amounts of weight. Table 1 presents the 85% weights of rats both before and after ad libitum diet exposure. Weights did not differ between groups either before, $F(1, 28) = 0.62$, $p = .437$, or after, $F(1, 28) = 2.36$, $p = .136$, exposure to HF or CTL diets.

Extinction

Figure 1B shows responding over the course of extinction. Rats in all groups extinguished responding, but there was some evidence that conditioned responding established in acquisition was more context-specific in rats fed the HF diet: HF rats showed lower levels of responding in the Different context than in their original training (Same) context. Although neither the effect of context, $F(1, 28) = 3.53$, $p = .071$, nor the Context \times Diet interaction, $F(1, 28) = 2.40$, $p = .133$, was significant, an analysis of the simple main effects of context was significant for HF, $p = .022$, but not CTL, $p = .817$, rats. However, the apparently greater responding in HF-Same than in CTL-Same rats was not significant, $p = .150$. In addition, there was a significant main effect of session, $F(5, 140) = 32.71$, $p < .001$, but not of diet or any other

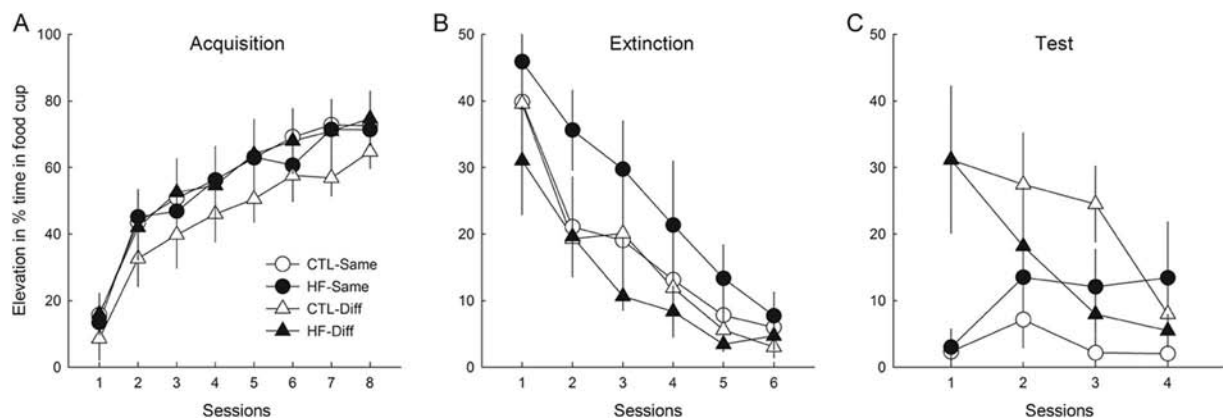


Figure 1. Elevation in responding during the acquisition, extinction, and test phases. Separate groups of rats received either a high-fat (HF) or control (CTL) diet after acquisition, and were extinguished in either the same context as acquisition (Same) or in a different context (Diff). Elevation scores were constructed by subtracting responding in the 5-s pre-conditioned stimulus periods from either responding during the last 5 s of the noise cue (acquisition) or from peak interval responding, the average of responding during the last 5-s period of cue presentation and the first 5 s after cue termination (extinction and test; see text for justification).

interactions, $ps > .400$. Finally, pre-CS responding did not differ among the groups ($2.1 \pm 0.7\%$ to $5.2 \pm 2.9\%$); ANOVA found only a main effect of session, $F(5, 140) = 5.25$, $p < .001$ (declining over sessions); other $ps > .360$.

Renewal Test

Figure 1C shows responding in the Same context in the four renewal test sessions. Initially, both HF and CTL rats showed substantial renewal of responding in the Same context after extinction and in the Different context. However, after the first four trials of test, renewal was significantly smaller in HF rats than in CTL rats. An overall Context \times Diet \times Session ANOVA showed significant main effects of context (the renewal effect), $F(1, 28) = 9.23$, $p = .005$, and session, $F(3, 84) = 3.07$, $p = .032$. Furthermore, the Context \times Session interaction was significant, $F(3, 84) = 5.48$, $p = .002$, and the Context \times Diet interaction was marginally significant, $F(1, 28) = 3.08$, $p = .090$. ANOVA of responding in the first test alone showed only a main effect of context, $F(1, 28) = 13.78$, $p < .001$; other $ps > .962$. By contrast, ANOVA of responding over the remaining three test sessions showed only a marginally significant main effect of context, $F(1, 28) = 3.52$, $p = .071$, but a significant Context \times Diet interaction (indicating that renewal was affected by diet), $F(1, 28) = 6.52$, $p = .016$, as well as a significant main effect of session, $F(2, 56) = 3.62$, $p = .033$. Individual comparisons showed significantly greater responding in CTL-Diff rats than in CTL-Same rats, $p = .004$, but no difference in responding between the two HF groups, $p = .964$. Thus, over Tests 2–4, rats exposed to the CTL diet displayed renewal but rats exposed to the HF diet did not. Indeed, although HF-Diff rats showed marginally *less* responding than CTL-Diff rats, $p = .078$, HF-Same rats showed marginally *more* responding than rats in the CTL-Same group, $p = .085$.

Finally, comparable ANOVAs of pre-CS responding, which ranged between $5.4 \pm 3.2\%$ and $9.3 \pm 4.6\%$ overall among the four groups, showed no significant effects, $ps > .222$.

Discussion

Exposure to a high-fat diet after the completion of training affected the nature of extinction. Although control rats extinguished in a context other than their training context showed substantial renewal of extinguished responding when tested in the training context, rats exposed to a high-fat diet showed considerably less persistent renewal. Thus, exposure to high-fat diet reduced the context-specificity of extinction. Because HF rats differed from CTL rats primarily in their exposure to saturated fat, this effect is attributable to short-term high-fat exposure and not to exposure to a high-energy food, caloric intake, or weight gain.

Other aspects of the data are informative about the origins of this effect. First, it is unlikely that the reduced context-specificity of extinction in HF rats was the result of impaired pattern separation: HF rats showed a larger effect of context change between training and extinction on the display of previously trained CRs, compared with CTL rats. Alterations in a unitary pattern separation mechanism could not account for both more sensitivity of initial learning to context change and less sensitivity of extinction learning. Second, the lower responding of HF-Diff rats in the renewal test is not attributable to generally stronger extinction learning or

weaker excitatory learning. In both extinction and test phases, HF rats extinguished in the training context showed (nonsignificantly) more responding than similarly extinguished CTL rats. Thus, the greater context generality of extinction in HF rats was observed despite (nonsignificant) evidence suggesting that extinction learning was generally weaker in HF rats.

The most plausible account for these data is that high-fat exposure reduces the contextual control of inhibitory learning. Although HF rats were sensitive to the context shift, they were impaired in using contextual information to mediate inhibitory learning acquired in extinction. This is supported by observations (Kanoski et al., 2010) that exposure to a high-fat diet impaired performance on a serial feature-negative “occasion-setting” discrimination, sometimes viewed as a model of contextual control (Bouton & Nelson, 1994; Grahame, Hallam, Geier, & Miller, 1990; Holland & Bouton, 1999). In this task, a tone CS was reinforced by food unless it was preceded by a light cue. HF rats, like rats with hippocampal lesions (Holland, Lamoureux, Han, & Gallagher, 1999), failed to suppress responding on nonreinforced trials, as if they were unable to use the information provided by the light to set the occasion for nonreinforcement of the tone.

Although consumption of saturated fat is associated with cognitive deficits, the causes and mechanisms by which these effects are produced are not well understood. The effects of saturated fat on hippocampal-dependent learning in rats have been linked to elevated triglyceride levels (Farr et al., 2008), increased permeability of the blood–brain barrier (Kanoski et al., 2010), and reductions in brain-derived neurotrophic factor (BDNF; Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). The effects of high-fat diets on inhibitory control also suggest influences on function of the prefrontal cortex; notably, high-fat diets reduce BDNF and plasticity in both prefrontal cortex and hippocampus (Kanoski et al., 2007).

Considerable evidence indicates that overeating, even while food satiated, can come under the control of discrete and contextual cues that have been paired with food consumption while deprived of food (Bouton, 2011; Holland & Petrovich, 2005; Petrovich, Ross, Gallagher, & Holland, 2007; Todd, Winterbauer, & Bouton, 2011). Furthermore, through learning, deprivation states themselves may come to control such behavior (e.g., Davidson, 1993). Individuals must learn that food is rewarding in certain contexts but not in others, such as in the presence of external (a predator) or internal (satiety signals) cues. Both hippocampus (Chan, Morell, Jarrard, & Davidson, 2001) and medial prefrontal cortex (Petrovich, Ross, Holland, & Gallagher, 2007) have been implicated in this learning. By interfering with normal acquisition of contextual control, exposure to high-fat diets may encourage such overeating in inappropriate environmental or motivational contexts.

Renewal often serves as a model of relapse. For example, extinction-based psychotherapies for localized anxiety disorders or substance abuse are typically conducted in settings that are quite different from the contexts in which the maladaptive learning was acquired. The reappearance of undesirable learned behaviors when treated individuals return to their normal lives is highly likely across a range of treatments, as even massive extinction does not typically eliminate renewal effects (Rosas, Garcia-Gutierrez, & Callejas-Aguilera, 2007; but see Denniston, Chang, & Miller, 2003). Procedures that enhance the transfer of therapeutic extinction learning to original learning contexts, such as using multiple extinc-

tion contexts, reduce renewal or relapse (Bouton, 2002; Chelonis, Calton, Hart, & Schachtman, 1999; Gunther, Denniston, & Miller, 1998). However, even the effectiveness of using multiple extinction contexts in reducing relapse is attenuated when training also occurs in multiple contexts (Bandarian Balooch & Neumann, 2011). Anxiety, fear, drug addiction, and overeating occur in many contexts, so substantial and permanent attenuation of relapse may be difficult, even when multiple extinction contexts are used. An interesting implication of our results is that consumption of diets high in saturated fat may aid in the generalization of therapeutic practices meant to treat these aspects of phobia, drug addiction, and overeating.

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