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The effect of dietary intervention on the metabolic and behavioural impairments generated by short term high fat feeding in the rat

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HIGHLIGHTS

- The effects of 3–4 weeks high fat feeding (HFF) on rat behaviour were investigated.
- HFF reduced lever-pressing rates and response flexibility in a demanding operant task.
- HFF did not impair selection of a large reward in second less demanding operant task.
- Restoration to a normal diet attenuated the behavioural deficits evoked by HFF.
- A deficit in motivation persisted following restoration to a normal diet.

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ABSTRACT

Previous studies have shown that rats fed a high calorie diet rich in saturated fat for 12 weeks exhibit peripheral insulin resistance and impairments of behavioural flexibility when switched from an operant delayed matching to place (DMTP) schedule to a delayed non-matching to place (DNMTP) schedule. However, the metabolic changes evoked by feeding a high fat (HF) diet can be observed within two weeks of commencing the diet. The current study has confirmed that 4 weeks exposure to an HF diet resulted in increased body weight, peripheral insulin resistance and plasma leptin. Studies performed during weeks 3 and 4 on the HF diet revealed suppressed lever pressing rates and impaired behavioural flexibility in the operant DMTP/DNMTP task. When animals fed the HF diet were then returned to a standard chow (SC) diet for 5 weeks their weight and blood biochemistry no longer differed from those measured in animals that had never been exposed to the HF diet. The animals restored to the SC diet exhibited a clear ability to acquire the DNMTP schedule of reinforcement although these animals continued to lever press at a lower rate when compared with animals that received the SC diet throughout. The data suggest that exposure to an HF diet diminishes the motivation to respond for a reward and, thus, the capacity to adapt behavioural performance. This deficit was ameliorated, but not totally reversed, by the dietary intervention. If also true for humans, the results suggest that deficits in behavioural flexibility develop after only a short period on a high calorie diet but may be largely reversible through simple dietary intervention, at least in the early stages of deficit development. However, the putative effects of short-term exposure to an HF diet on behavioural motivation may persist for some time after switching to a healthier low fat diet and remain a problem for those seeking to adopt a healthier diet.

1. Introduction

There is now compelling evidence that the consumption of high calorie western diets that are rich in sugar and saturated fat can have adverse effects of cognitive function and memory (for review see [1]). To some extent, these deficits may be related to the development of obesity, insulin insensitivity and type 2 diabetes that are commonly associated with chronic exposure to these diets [2,3]. However, there is evidence that some impairments of cognitive function are not directly associated with the changes in metabolic control and weight gain that this type of diet can cause [1,2]. The putative impairments of learning and memory evoked by the development of obesity and insulin resistance have also been explored using animal models. These studies provide further support for the hypothesis that exposure to a

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calorie-rich diet is associated with cognitive impairment but they do not provide definitive insights into the possible roles of insulin resistance or the other metabolic and hormonal changes evoked by exposure to diets of this type [4–6]. Some studies have provided support for a link between changes in insulin signalling and diet-induced behavioural deficits while others have not [2,3,7].

Previous studies in our laboratory have shown that rats fed a high calorie diet, rich in saturated fat, evoked a specific effect in behavioural responding in animals trained to lever press in an operant variable delay non-matching to position (DNMTP) task [8]. The animals were initially trained to perform the DMTP task before being exposed to the HF diet. When re-tested on the task after 9 weeks of high fat (HF) feeding there was a modest reduction in the accuracy of responding in this task when compared with animals fed a standard chow (SC) diet. However, when the animals were switched to a non-matching to position (DNMTP) task, a more profound impairment was observed. In our original study, the behavioural deficits measured in HF fed rats tested in the operant task correlated negatively with the plasma insulin concentration and the fasting insulin resistance index (FIRI) although a subsequent study suggested that this might not represent a causative relationship [9].

In our earlier studies, the behavioural tests were performed in animals fed the HF diet for 9 weeks. However, studies with human subjects suggest that deficits in reaction time and attention are apparent within 7 days of starting an HF diet [10]. Studies with rats have also suggested that consuming a diet high in fat and/or carbohydrate for only short periods impairs radial maze performance [11,12]. A primary objective of the current study, therefore, was to determine if feeding the HF diet employed in studies in our laboratory for a similarly short period of time had the same effects on the DMTP and DNMTP operant task as those seen in rats fed this diet for 9 weeks. The main experiment also sought to test this hypothesis further by exploring the consequences for behaviour of returning the animals to an SC diet following a period of HF feeding. Measurements of weight change, plasma leptin and peripheral insulin resistance were also performed to confirm that a short period of exposure to the HF diet elicited changes in these measures similar to those observed following more prolonged exposure to the diet and to examine whether these changes could be reversed by returning the HF-fed animals to the SC diet. Follow-on experiments sought to investigate putative mechanisms that may account for the deficits in the DMTP/DNMTP task evoked by the diet. These additional studies included a measure of spontaneous alternation as a test for changes in short-term working memory (experiment 1); measurements of spontaneous locomotor activity to determine if changes in responding in the operant task might reflect generalised changes in activity (experiment 2) and a study designed to determine if feeding the HF diet reduced spontaneous and operant-based measures of reward preference which might be indicative of reduced motivation to respond for a palatable reward (experiment 3).

2. Materials and methods

2.1. Subjects

All experiments used male Wistar rats (Harlan UK Ltd) with an initial body weight of 150–175 g. Animals were housed in cages of four under a 12 h:12 h light: dark pattern (holding room light on at 0600 h; off at 1800 h) at an ambient temperature of 22 ± 1 °C. Rats had *ad libitum* access to either standard rat chow (SC) or high fat diet (HF) except where stated otherwise. Water was freely available throughout the study. The rats were weighed weekly during the studies. All experimental procedures were sanctioned by the University of Dundee Ethical Review Process and were performed in accordance with UK Home Office regulations under the auspices of Project Licence PIL60/3766.

2.2. Diet

Cages of animals were randomly assigned to receive either the SC diet (RM1-SDS diets, UK; kcal composition, 7.4% crude fat, 17.5% crude protein, 75.1% carbohydrate) or the high fat (HF) diet (SDS 824053; kcal composition 45% crude fat, 20% crude protein, 35% carbohydrate). The carbohydrate and fat composition of the SC diet was rice starch (45% w/w), mixed sugars (4.5% w/w) and soya oil (2.71% w/w) whereas the HF diet contained rice starch (28.3% w/w), sucrose (10.5% w/w), lard (17.9% w/w) and soya oil (4.3% w/w). For operant training and testing the animals were maintained on a restricted food regimen (85% of the free feeding daily intake per cage) to motivate them to perform the tasks reinforced with a sweetened pellet reward. Food restriction was initiated at least 3 days prior to operant testing (experiments 1 and 3).

2.3. Behavioural experiments

2.3.1. Experiment 1: effects of HF feeding on behavioural flexibility and short-term-working memory

The operant experiments were performed in a bank of 8 operant chambers (Med Associates) using the protocol employed in our earlier studies [8]. The design of the experiment is summarised in Fig. 1 with details of the protocol provided below.

2.3.1.1. Habituation and training. Animals were maintained on a restricted food regime using the procedure adopted in our previous studies [8,9] Starting 3 days before training commenced, the amount of food available to the rats was reduced to 85% of the free feeding daily intake per cage. During free feeding the rats fed the SC diet consumed more food by weight (but not calorific value) than the rats fed the HF diet. Thus, during habituation and training food hoppers contained sufficient food to allow each SC-fed rat 21 g food per rat per day; the HF-fed animals were limited to 18 g of food per rat per day. During this period rats were habituated to the chambers and sucrose pellets. Following habituation animals were trained under a continuous reinforcement schedule (CRF) with the house light off. During this period both levers were extended and response on either lever was rewarded with delivery of a pellet. Each session was terminated after 40 min or when 100 pellets had been delivered. Criterion was set at 80 pellets over 3 consecutive days. On reaching criterion the animals progressed on to the next phase of training. During each trial only one lever was presented and this alternated between trials in a pseudorandom manner. Depression of the lever resulted in delivery of a sucrose pellet and retraction of the lever. Following a brief (5 s) inter-trial interval the opposite lever was presented. Training continued until a criterion of 80 correct responses over 3 consecutive days was achieved. Animals were then trained on a simple delayed matching to position (DMTP) task.

2.3.1.2. DMTP training and testing. Each DMTP session lasted for 40 min during which the house light remained off except in the case of an incorrect response (see below). The task began with a sample phase during which one lever was extended. This was predetermined by a computer programme so that both levers were presented approximately the same number of times. On depression of the sample lever, the lever retracted and an inter-trial interval (ITI, 5 s) began. The first nose poke of the central food hopper after the ITI initiated the choice phase during which both levers were extended and a correct response (*i.e.* the sample lever) was rewarded with a sucrose pellet. An incorrect response resulted in a 5 s "time out" period during which both levers were retracted, the house light illuminated and no reward was delivered. The levers remained extended until the rat responded on one of the levers. Once a criterion of >80% correct choices was achieved over 3 consecutive days, time delays of 0, 2, 4, 8, 12, 18 or 24 s were introduced at random between sample and choice phases.

Upon reaching asymptotic performance, rats were tested for 5 days (maximum of 100 rewards or 40 min) to provide baseline measurements.

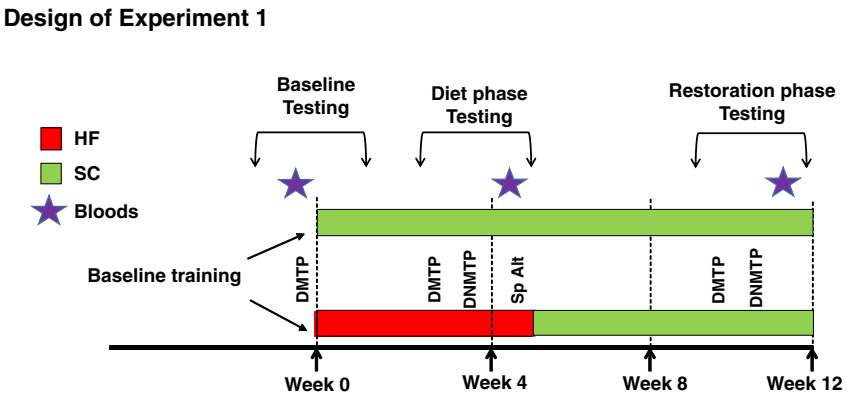

Fig. 1. Experimental design. Experimental design depicted as a time line detailing points of behavioural and metabolic testing.

On the next day the rats were divided into 2 groups ($n = 8$ per group) which were assigned to the SC or HF diet (see Fig. 1). Before commencing the diet, blood samples were collected for biochemical analysis. The groups were then fed the SC or HF diet respectively for 5 weeks. The animals were re-tested on the DMTP task during the 5 working days of week 3. At the beginning of week 4 the contingency was switched to a non-matching paradigm (DNMTP) that was identical to the DMTP task apart from during the choice phase where a response to the opposite lever from that extended during the sample phase was rewarded, whereas a response to the same lever resulted in a time out phase. Animals were tested for 5 days on the DNMTP task. Weeks 3 and 4 were defined as the "diet" phase for data analysis. On each day of operant testing, the number of lever-presses on both the correct lever that delivered the reward and the incorrect lever were recorded and the accuracy of responding (the percentage of responses made on the lever that delivered the reward) calculated. Response rates are expressed as lever-presses per minute. Blood samples were collected for biochemical analysis following completion of operant testing.

In order to test the hypothesis that any effects of HF feeding in the DMTP/DNMTP tasks might reflect impairments of spatial working memory, the animals were tested in a spontaneous alternation task during week 5, while they were still on their respective diets, using the procedure described by McNay and colleagues [13]. Briefly, rats were placed in the centre of a closed 4-arm maze and allowed to explore freely for 10 min. Activity was recorded and scored at a later date by two independent observers who were blind to the treatment the animals had received. An alternation was counted when a rat visited all 4 arms within a span of 5 arm choices. This was converted to a percentage by dividing the number of alternations by the total possible number of alternations [total number of alternations/(total arm entries − 4)]. The total number of arm entries during the trial was assessed as a measure of locomotor activity.

Starting at the beginning of week 6, the final part of the experiment explored the extent to which the behavioural impairments, evoked by HF feeding, could be ameliorated by restoring the HF-fed animals to the SC diet for 5 weeks. The animals fed the SC diet during weeks 1 to 5 remained on this diet. All the animals were retested on the DMTP and DNMTP tasks during weeks 10 and 11 of the study. The results generated by this part of the study are referred to as the "restoration" phase in the data analyses.

Plasma glucose, insulin and leptin were measured at baseline, during the diet phase (week 4) and during the restoration phase (week 11). The blood samples were taken from the saphenous vein of the hind limb following an overnight fast and after completion of behavioural testing. Plasma glucose was measured immediately from whole blood using an Accuread© hand monitor and additional samples collected into lithium-heparin coated microvette tubes (Sarstedt, UK). Following centrifugation plasma insulin and leptin were measured by ELISA (Insulin; Crystal Chem, Inc., IL, US; Leptin; R&D Systems) respectively. Fasting insulin resistance index (FIRI) was calculated from fasting glucose and insulin measurements using the formula $FIRI = [(F_0 \times F_I)/25]$ where F_0 = fasting glucose measured in mmol/l and F_i = fasting insulin measured in μU.

2.3.2. Experiment 2: effects of the HF diet on locomotor activity

In order to test the possibility that any changes in the rate of lever pressing observed in the HF-fed rats in experiment 1 might reflect a generalised change in activity, spontaneous locomotor activity was examined in a separate cohort of rats. Groups of rats ($n = 6$ per group) were fed the HF or SC diet for 4 weeks. At the end of week 4, the rats were placed in the centre of a Perspex activity box (Med Associates; 43 cm square with 31 cm sides) for a period of 20 min. Activity was recorded automatically using a grid of infra-red transmitters and receivers.

2.3.3. Experiment 3: effects of the HF diet on sucrose preference and operant responding for large and small rewards

This experiment tested the possibility that feeding an HF diet influences the ability to discriminate between a large and small palatable sweetened reinforcer. A third cohort of rats was initially trained in the same operant chambers as experiment 1 to press either lever to gain a single sweetened pellet reward. During training the animals were restricted to 85% of their normal level of food consumption. The levers were presented in response to a nose-poke in the central pellet dispenser and retracted after each lever press. Nose-pokes within 10 s of the last reward had no programmable consequences and this period was signalled by illumination of the house-light. Once the rats reached criterion of gaining 80 rewards or more using both levers for 2 consecutive days they were assigned to one of two groups ($n = 8$ per group) to be fed the SC or HF diets for the remainder of the experiment.

Before commencing the diet, a sucrose preference trial was performed to determine a baseline measure of preference for a sucrose solution over water. Each rat was placed singly into a cage at 1900 h with restricted access to food (see Section 2.2). At 0900 h on the following day, the animals were presented with two weighed bottles for 60 min. One bottle contained tap water; the other contained a 0.8% (w/v) solution of sucrose in tap water. The volume of water and sucrose solution consumed by the rats were measured by weighing the weight of the drinking bottle and the preference calculated as the percentage of the total weight consumed taken from the sucrose bottle. The volumes of the sucrose solution and tap water consumed in these tests were recorded and expressed as the preference for the sucrose solution. A sucrose preference trial was also repeated at the end of the operant component of the experiment.

The animals were then returned to group housing and the diet started. After 18 days of free feeding they were again restricted to 85% free feeding food allowance and trained for two days on a forced choice operant schedule in which each nose-poke resulted in the presentation

of either the left or the right lever. Responding on one of the levers delivered a small reward (1 sweetened pellet as used during initial training) or a larger reward (5 sweetened pellets). The lever that delivered the large reward (left or right) was balanced across the two groups. During the next week, the animals were tested on a schedule that consisted of 5 cycles of trials containing presentation of either lever at the beginning as a reminder followed by a choice of levers for 6 trials. Pressing levers resulted in the delivery of the appropriate reward, the retraction of the lever and house light illumination for 10 s. The house light was then extinguished and the next nose-poke resulted in the alternate lever appearing. Pressing this lever resulted in the delivery of the reward assigned to the lever, the lever being retracted and the house light being illuminated for 60 s. During 6 choice trials a nose-poke resulted in both levers appearing. A lever response within 10 s resulted in the delivery of the assigned reward, both levers being retracted and the house light being illuminated for 60 s. Total responses on the levers delivering the larger and smaller rewards were recorded. No response within 10 s caused retraction of the levers and 60 s of a time out with the house light on. This was recorded as a non-response. During the daily sessions in the following week the reward value of the levers was reversed.

2.4. Data analyses

Most of the results satisfied the criteria for parametric analysis. These data are presented as mean ± SEM and were analysed by analysis of variance (ANOVA) for repeated measures or a one-way ANOVA when no repeated measures were made. *Post hoc* analyses were performed using a Bonferroni or *t*-test as appropriate. In the DMTP/DNMTP study (experiment 1), the maximum number of rewards the rats could receive was fixed at 100. The data for total rewards received are presented as means and were analysed non-parametrically using the Freidman test for repeated measures. The Mann–Whitney *U* test was used to determine differences between the groups. Significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 21.0.

3. Results

3.1. Experiment 1 - effects of HF feeding on behavioural flexibility and short-term working memory

3.1.1. Physiological responses to the HF diet

Body weight and blood biochemistry measures at baseline, week 4 and week 11 are shown in Fig. 2. Statistical analysis of body weight, using diet (SC or HF) as the between subjects factor and experimental phase (baseline, diet and restoration) as the within subject factor revealed a significant interaction between diet and experimental phase ($F_{2,28} = 20.2$, $p < 0.01$). *Post-hoc* analysis confirmed that the group consuming the HF diet were significantly heavier than the SC group at week 4 ($p < 0.01$) but not at baseline or week 11 (Fig. 2A). Fasting plasma glucose was not influenced by HF feeding or restoration to the SC diet but did increase significantly ($F_{2,28} = 16.1$, $p < 0.01$) with the duration of the study (Supplementary Table 1). The analysis of fasting plasma insulin levels revealed a significant interaction of diet with experimental phase (diet × experimental phase ($F_{2,28} = 4.27$, $p < 0.05$). *Post hoc* analysis revealed a significant increase in the HF group at week 4 ($p < 0.05$) but no difference at baseline or week 11 (Supplementary Table 1B). The FIRI also revealed a significant interaction between diet with experimental phase (diet × experimental phase $F_{2,28} = 4.35$, $p < 0.05$) and again the HF diet group had a significantly elevated FIRI at week 4 ($p < 0.01$) whereas there was no difference at baseline or week 11 (Fig. 2B). Analysis of the fasting plasma leptin values revealed significant effects of diet ($F_{1,13} = 13.8$, $p < 0.01$), experimental phase ($F_{2,26} = 2580$, $p < 0.01$) and an interaction between the two ($F_{2,26} = 9.0$, $p < 0.001$). *Post hoc* analysis confirmed that the leptin levels were significantly higher in the group consuming the HF diet at week 4 but not baseline or week 11 (Fig. 2C). Additionally plasma leptin concentrations for both groups were higher ($p < 0.01$) in week 11 when compared with baseline.

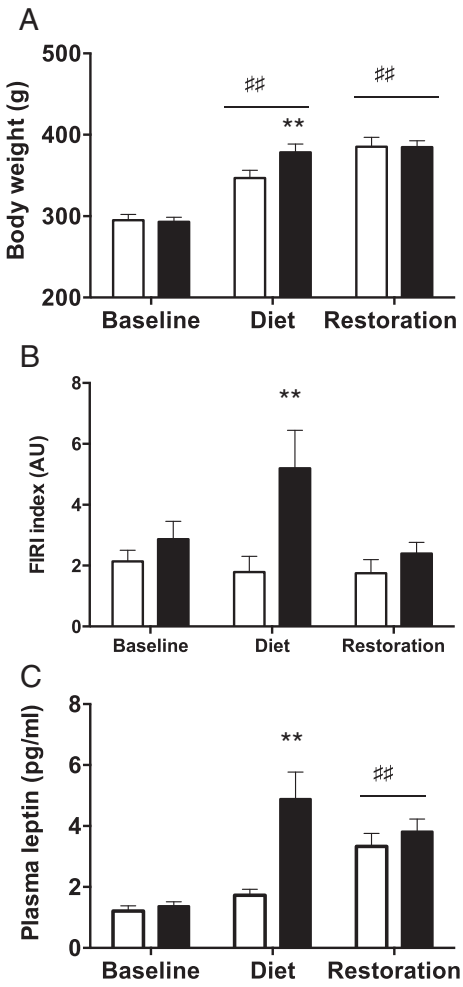

Fig. 2. Physiological responses to the high fat diet. The animals were fed either standard laboratory chow (SC) or the high fat diet (HF) for 5 weeks (diet phase). All animals were fed the SC diet for the remainder of the study (restoration phase). Panel A shows body weights, panel B the fasting insulin resistance index (FIRI) and panel C plasma leptin concentrations measured at baseline (week 0), at the end of week 4 and the end of week 11. The FIRI was calculated using the formula [(fasting glucose × fasting insulin)/25] and is presented in arbitrary units (AU). The data are presented as means ± SEM; ($n = 8$ for each group). The open columns summarise the results for the SC-fed rats; the filled columns summarise the results for the HF-fed rats. Significantly different from SC rats $^{**} = p < 0.01$; significantly different from baseline $^{\#\#} = p < 0.01$.

In summary, the HF group had significantly increased body weight, plasma insulin, FIRI and plasma leptin levels at week 4 relative to the SC group when they were on the HF diet but not week 11 when they had been restored to the SC diet for 5 weeks.

3.1.2. Operant measurements of DMTP and DNMTP

3.1.2.1. Analysis of the DMTP task. At completion of training all the animals performed the DMTP task and exhibited a preference for the correct (rewarded) lever that exceeded 80% of total lever presses. A global analysis of the lever pressing rates across the 3 phases of the study (baseline, diet and restoration phases) showed that the lever pressing rates were not influenced by the inter-trial delay. However, the pressing rates were influenced by the diet ($F_{1,14} = 16.7$; $p < 0.001$), the experimental phase ($F_{2,28} = 55.8$; $p < 0.001$), the lever selection ($F_{1,14} = 174.3$; $p < 0.001$) and test day ($F_{4,56} = 5.3$; $p < 0.001$). Additionally, there was a significant 4-way interaction

between these factors (diet × experimental phase × lever × test day $F_{8,112} = 9.8$; $p < 0.001$). A second analysis of the lever preference data (calculated as the percentage of total responses made on the rewarded (correct) lever showed that lever preference was influenced by phase ($F_{2,28} = 14.0$; $p < 0.001$), test day ($F_{4,56} = 46.6$; $p < 0.001$) and that there was a significant 3-way interaction between phase, diet and test day (diet × experimental phase × test day $F_{8,112} = 10.7$; $p < 0.001$). The inter-trial delay again had no significant effect.

Post hoc analysis showed that during the baseline phase of the study, the lever pressing rates on each of the levers were statistically comparable between the rats subsequently assigned to the SC control group and those subsequently assigned to the HF group (Fig. 3A & B). However the animals showed a marked preference for the correct lever ($F_{1,14} = 8194.9$; $p < 0.001$). At baseline, this measure did not differ significantly between the two groups of animals (Fig. 3C). All the animals when tested during this phase completed with trial within the 40 min maximum and, thus, gained 100 rewards on each test day.

When the SC animals were re-tested in the second (diet) phase of the experiment, the pressing rate on the correct lever was significantly lower than that measured during the baseline phase ($F_{1,4} = 20.0$; $p < 0.01$). This reduction was influenced by test day (experimental phase × test day $F_{4,28} = 11.3$: $p < 0.001$). *Post hoc* analysis showed that the reductions ($p < 0.01$) occurred on test days 2, 3 and 4 only. By contrast, the pressing rate on the correct lever exhibited by the HF-fed animals was consistently reduced when compared with the rate measured for this group of animals during the basal phase of the study ($F_{1,4} = 36.7$; $p < 0.001$). During the diet phase of the experiment (week 3) the SC-fed and HF-rats responded at a higher rate on the correct lever than the incorrect lever ($F_{1,4} = 123.1$; $p < 0.001$ for SC rats; $F_{1,4} = 79.1$; $p < 0.001$ for HF rats) confirming that both groups continued to discriminate between the levers. Further analysis showed that HF-animals made fewer responses per minute on the correct lever than the SC-fed animals ($F_{1,14} = 49.1$; $p < 0.001$; Fig. 4A). They also responded at a lower rate on the incorrect lever ($F_{1,14} = 17.5$; $p < 0.01$; Fig. 4B). *Post hoc* analysis revealed that preference for the correct lever was not influenced significantly by the diet the animals had received (Fig. 4C). In contrast to the SC group of animals, none of the HF-fed rats completed the task (*i.e.* gain 100 rewards) within 40 min and, as result this group consistently gained fewer rewards ($p < 0.001$) than the SC-fed rats (Fig. 5A).

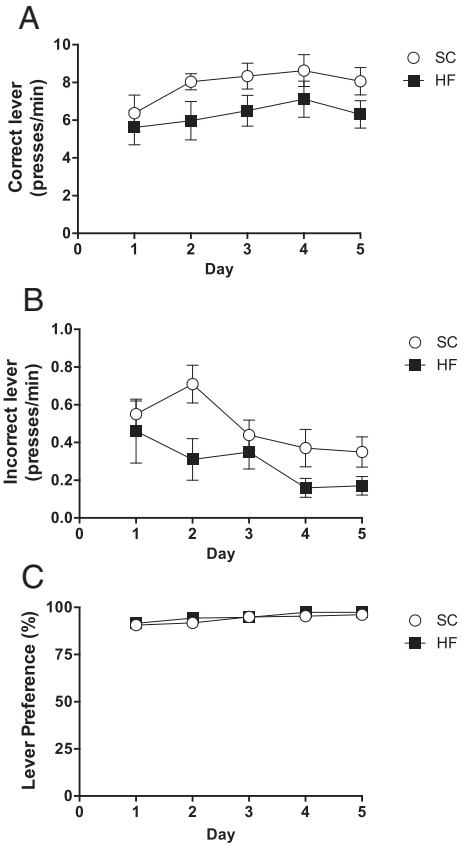

Fig. 3. Baseline behavioural measures prior to commencing the HF diet. The animals were tested on the operant DMTP task for 5 days prior to commencing the HF diet. The data are presented as mean ± SEM (n = 8 for each group). The open circles show the results for the rats that were subsequently fed the SC diet; the closed circles show the results for the rats that subsequently fed the HF diet. Panel A shows the mean pressing rate (presses/min) on the correct (rewarded) lever; panel B shows the mean pressing rate on the incorrect (non-rewarded) lever; panel C shows the mean preference for the reward lever.

When tested in the third (restoration) phase of the experiment, the mean rate of responding on the correct lever on the DMTP schedule exhibited by the HF-SC restored animals was significantly was higher ($F1,4 = 9.8$; $p < 0.05$) than the rate measured for the diet phase of the experiment when the rats were on the HF diet, but remained significantly different ($F_{1,14} = 5.9$; $p < 0.05$) to that exhibited by the animals which had never been exposed to the HF diet (Fig. 6A). This effect interacted significantly with test day (diet × test day $F_{4,56} = 10.3$; $p < 0.001$). *Post hoc* analysis showed that on test day 1, the HF-SC restored group pressed more frequently ($p < 0.05$) on this lever than the SC group of animals whereas on subsequent test days they pressed at a significantly lower rate ($p < 0.05$) than the SC rats. The rate of responding exhibited by the HF-SC restored rats on the incorrect lever was also lower than the response rate on this lever exhibited by the SC-fed rats ($F_{1,14} = 20.4$; $p < 0.001$). This effect also interacted significantly with test day (diet × test day $F_{4,56} = 11.3$; $p < 0.001$). *Post hoc* analysis showed that the rate of responding on this lever was only significantly reduced in the HF-SC restored rats on test day 1 on this schedule (Fig. 6B). The numbers of rewards gained by both the SC- and HF-fed rats were consistently close to 100 although there was a trend for the number of rewards gained by the HF-fed rats to be marginally lower than those gained by the SC-fed animals (Fig. 5C). This effect reached statistical significance on test days 2 and 3 ($p < 0.01$) and 4 ($p < 0.05$). Lever preference on the DMTP schedule was influenced by diet ($F_{1,4} = 17.5$; $p < 0.01$) and test day ($F_{4,56} = 56.7$; $p < 0.01$) and these two effects interacted significantly (diet × test day $F_{4,56} = 17.9$; $p < 0.01$). *Post hoc* analysis showed that the preference of the HF-SC restored rats was higher on test day 1 than the preference exhibited on this day by the control rats fed throughout with the SC diet (Fig. 6C). Thereafter, the preferences were not significantly different.

In summary, both the SC- and HF-fed animals were able to recall the DMTP task as measured by their preference for the correct lever. However, HF feeding resulted in a reduction in the rate of lever pressing on both the correct and incorrect levers and this was associated with a reduction in the number of rewards gained by this group of rats. A reduced rate of lever pressing on the correct lever was also observed following restoration of the SC diet to the HF group of animals although this was not sufficiently large to cause a marked reduction in the number of rewards gained by this group of rats.

3.1.2.2. Analysis of the DNMTP task. The animals were only tested on this contingency during the diet and restoration phases of the study. A global of the data for these two phase showed that lever pressing rates were influenced by diet ($F_{1,14} = 40.6$; $p < 0.001$), the experimental phase ($F_{1,14} = 79.0$; $p < 0.001$) lever selection ($F_{1,14} = 30.1$; $p < 0.001$) and test day ($F_{4,56} = 22.0$; $p < 0.001$). There was also a significant 3-way interaction between the effects of experimental phase, the lever selected and diet (experimental phase × lever × diet $F_{1,14} = 18.2$; $p < 0.001$). An analysis of the lever preference data for the two phases showed that this measure was influenced by experimental phase ($F_{1,14} = 292.1$; $p < 0.001$), diet ($F_{1,14} = 14.5$; $p < 0.01$) and test day ($F_{4,56} = 195.3$; $p < 0.001$). There was a significant 3-way interaction between the effects of these three factors (diet × experimental phase × test day $F_{4,56} = 6.9$; $p < 0.001$).

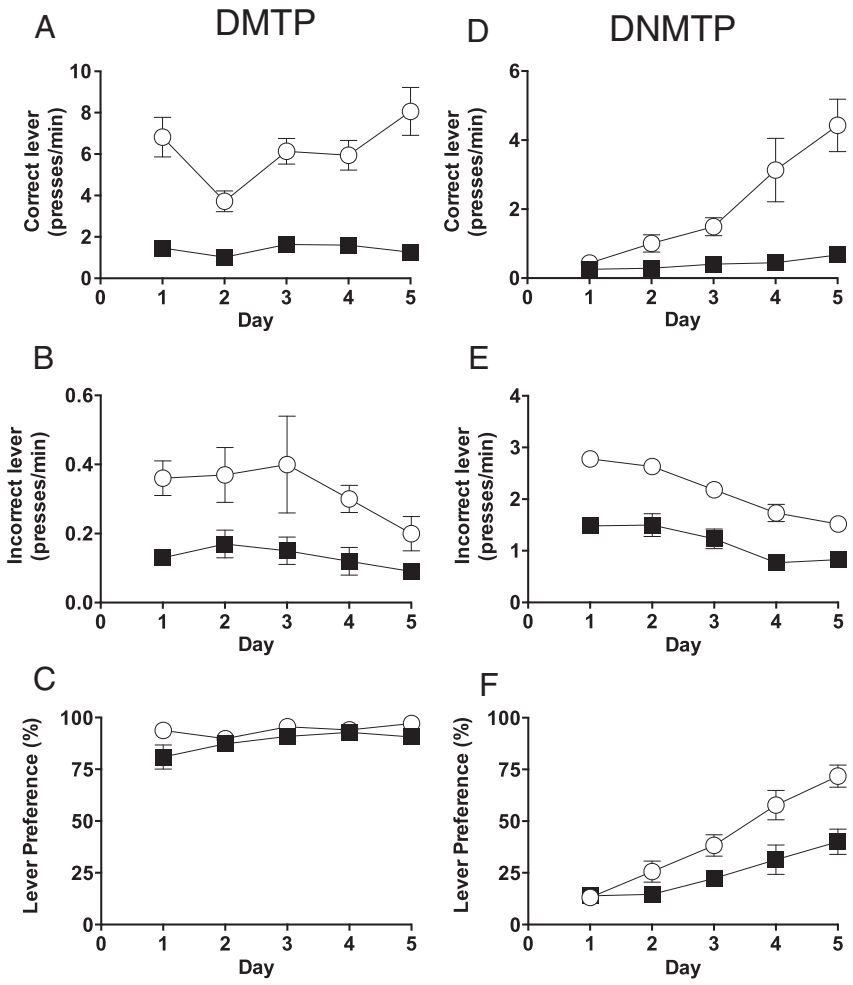

Fig. 4. Effect of diet on performance of the operant DMTP/DNMTP task. The animals were tested on the operant DMTP task for 5 days during week 3 while on the SC or HF diet and then switched to DNMTP paradigm for a further 5 days during week 4. The data are presented as means ± SEM ($n = 8$ for each group). The open circles show the results for the SC-fed rats; the closed circles show the results for the HF-SC restored rats. Panels A and D show the mean pressing rate (presses/min) on the correct (rewarded) lever; panels B and E show the mean pressing rate on the incorrect (non-rewarded) lever; panels C and F show the mean preference for the reward lever.

As anticipated, in the diet phase of the study on the first day that the contingency was changed to DNMTP, the rats continued to press on the lever they had been trained to press (the now incorrect lever) and made relatively few responses on the newly assigned correct lever. However, the response rate on the correct lever increased with test day ($F_{4,56} = 18.1$; $p < 0.001$) whereas the response rate on the incorrect lever decreased with days ($F_{4,56} = 25.9$; $p < 0.001$). As a result, the number of rewards received by the rats increased over the 5 trials ($p < 0.001$ for SC rats; $p < 0.01$ for HF rats). The increase in the rate of response on the correct lever following the switch in contingency interacted significantly with diet (contingency × diet × test day $F_{4,56} = 12.4$; $p < 0.001$), the HF rats responding at a lower rate on this lever than the SC-fed animals ($p < 0.05$ for days 2 to 4; $p < 0.001$ for day 5) on all the days tested except day 1 (Fig. 4D). As a result, the HF animals received fewer rewards ($p < 0.01$ or $p < 0.001$) on days 2 to 5 on this schedule when compared with their SC counterparts (Fig. 5B). Further analysis showed that the HF-fed animals also responded less frequently on the incorrect lever than the SC-fed animals ($F_{1,14} = 52.1$; $p < 0.001$; Fig. 4E). On the first day of the DNMTP schedule, the preference for the new correct lever fell to approximately 14% (Fig. 4F). Main effects analysis showed that the preference for the new correct lever increased with test day ($F_{4,56} = 55.1$; $p < 0.01$). This effect interacted significantly with diet (diet × test day $F_{4,56} = 7.6$; $p < 0.01$). *Post hoc* analysis revealed that the HF animals exhibited a significantly reduced preference for the correct lever on test days 3, 4 and 5 when compared with the SC-fed animals (Fig. 4F).

When, in the restoration phase of the study, the rats were once again switched to the DNMTP schedule, they initially responded at a higher rate on the lever that had been correct on the DMTP schedule. However, responding on the newly assigned correct lever increased with test day ($F_{4,56} = 34.8$; $p < 0.001$; Fig. 6D) whereas the rate of responding on the non-rewarded (newly assigned incorrect) lever diminished with test day ($F_{4,56} = 27.0$; $p < 0.001$; Fig. 6E). These changes were reflected by an increase in the numbers of rewards gained by the rats over the 5 daily trials ($p < 0.001$ for both SC and HF rats; Fig. 5D). When compared with the SC-fed rats, the response rate on the newly assigned correct lever, but not the newly assigned incorrect lever, exhibited by the HF-SC restored group of rats was consistently significantly lower than the rate exhibited by the SC control group ($F_{1,14} = 32.1$;$P < 0.001$). In spite of this reduced rate of responding, by test day 4 the number of rewards gained by the HF-fed rats (Fig. 5D) was only significantly different to those gained by the SC-fed rats on test days 1 to 3 ($p < 0.01$; $p < 0.001$; $p < 0.05$ respectively). Main effects analysis of the lever preference data (Fig. 6F) showed that HF-SC restored rats exhibited a lower preference for the correct lever than the preference exhibited by the SC-fed rats ($F_{1,14} = 14.3$; $p < 0.01$) but that this effect interacted significantly with test day (diet × test day $F_{4,56} = 3.6$; $p < 0.05$). *Post hoc* analysis revealed that the preference for the correct lever exhibited

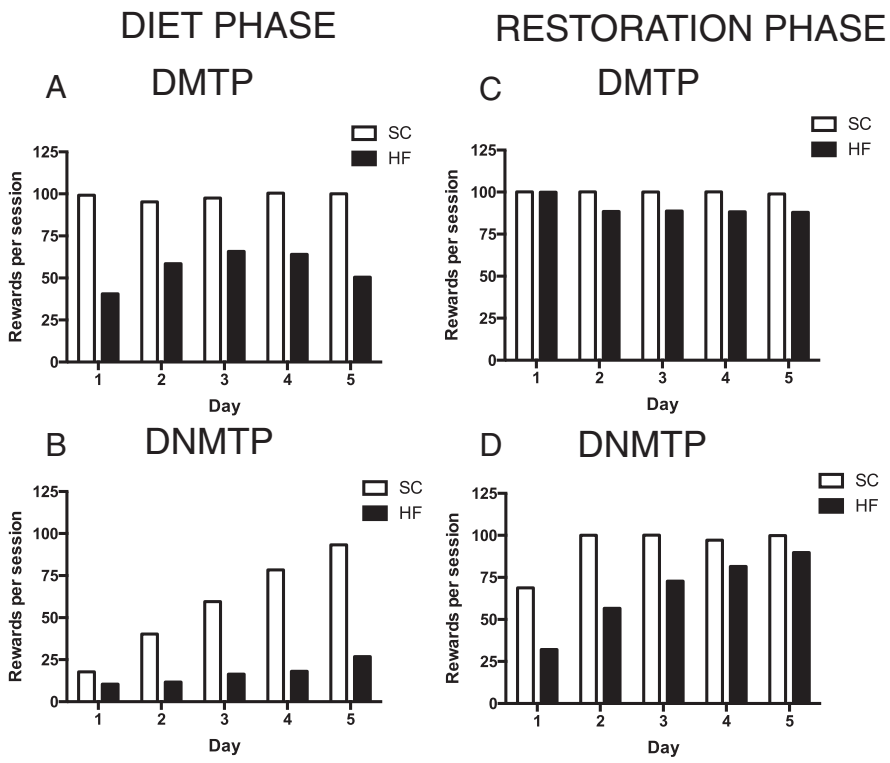

Fig. 5. Reward pellets consumed during the DMTP/DNMTP. The plots show the mean numbers of reward pellets presented to the rats in the DMTP/DNMTP operant experiments during the diet phase of study (left hand panels) and during the restoration phase (right hand panels).

by the HF-SC restored rats was statistically lower ($p < 0.05$) on test days 1–3.

In summary, when the contingency was changed to DNMTP for the first time during the diet phase of the study the preference of the SC animals for the new correct lever increased from approximately 14% to approximately 70% of total presses over the 5 days of testing. By contrast, the preference of the HF-fed rats for the new correct lever never exceeded 40% of total presses during the 5 days of testing. When retested during the restoration phase of the experiment, the performance of the SC rats on test day 2 (lever preference and rewards gained) was equivalent to that achieved by test day 5 during the diet phase. The HF-SC rats also appeared to be able to acquire the DNMTP task effectively, their performance as assessed using the same criteria, was similar to the rats fed the SC diet throughout by the final day of testing. However, this group of animals continued to respond a lower rate on the correct lever when compared with the rats that had been fed the SC diet throughout.

3.1.3. Spontaneous alternation

All the rats were tested in this paradigm while they remained on their SC or HF diets respectively. HF feeding had no significant effects on spontaneous alternation (Fig. 7A) or the total number of arm entries when compared with SC-fed controls (Fig. 7B).

3.2. Experiment 2 - effect of HF feeding on locomotor activity

Four weeks exposure to the HF diet had no significant effect on locomotor activity when measured in an activity box for 20 min (SC activity = 1314 ± 270 ambulatory counts; HF activity = 1507 ± 291 ambulatory counts).

3.3. Experiment 3 - effect of HF feeding on sucrose preference and operant responding for large and small rewards

At baseline, prior to starting the diet, the mean volume of fluid taken by the rats during the 1 h sucrose preference trial was 6.53 ± 0.65 ml of which 75.2 ± 3.6% was from the sucrose solution. At the end of the period on the diet, the SC-fed animals drank 6.13 ± 0.58 ml with a preference for the sucrose solution of 74.9 ± 3.6%. These values were not significantly different to those for the rats fed the HF diet (volume = 6.29 ± 0.04 ml; sucrose preference = 73.7 ± 4.8%).

The results of the operant preference task showed that feeding the HF diet had no significant effects on the total number of small or large rewards gained by the HF-fed rats in either the test or reversed contingency (Fig. 8 panels A,B,D and E). A global analysis of the lever preference data showed that preference for the lever that was reinforced with the larger reward increased with test day ($F_{4,56} = 30.78$; $p < 0.01$) but that this effect interacted significantly with the experimental contingency (test day × experimental contingency $F_{4,56} = 23.37$; $p < 0.01$). During the test phase of the experiment, preference for the lever reinforced by the larger reward exhibited by the SC-fed rats increased from 78 ± 8% to 89 ± 5% (Fig. 8C). Preference for the lever that delivered the larger reward was not influenced significantly by the diet fed to the rats. When the contingency was reversed, the rats initially responded on the lever that had previously delivered the larger reward. However, over the 5 day test period, responding on the lever that now delivered the small reward fell significantly ($F_{4,56} = 21.54$; $p < 0.001$; Fig. 8D) whereas responding on the lever that now delivered the larger reward increased significantly ($F_{4,56} = 32.58$ $p < 0.001$; Fig. 8E). As a result the preference for the larger reward in the SC rats increased from 14 ± 5% to 88 ± 4% over the same period (Fig. 8F). Feeding the HF diet had no significant effect on acquisition of the new contingency.

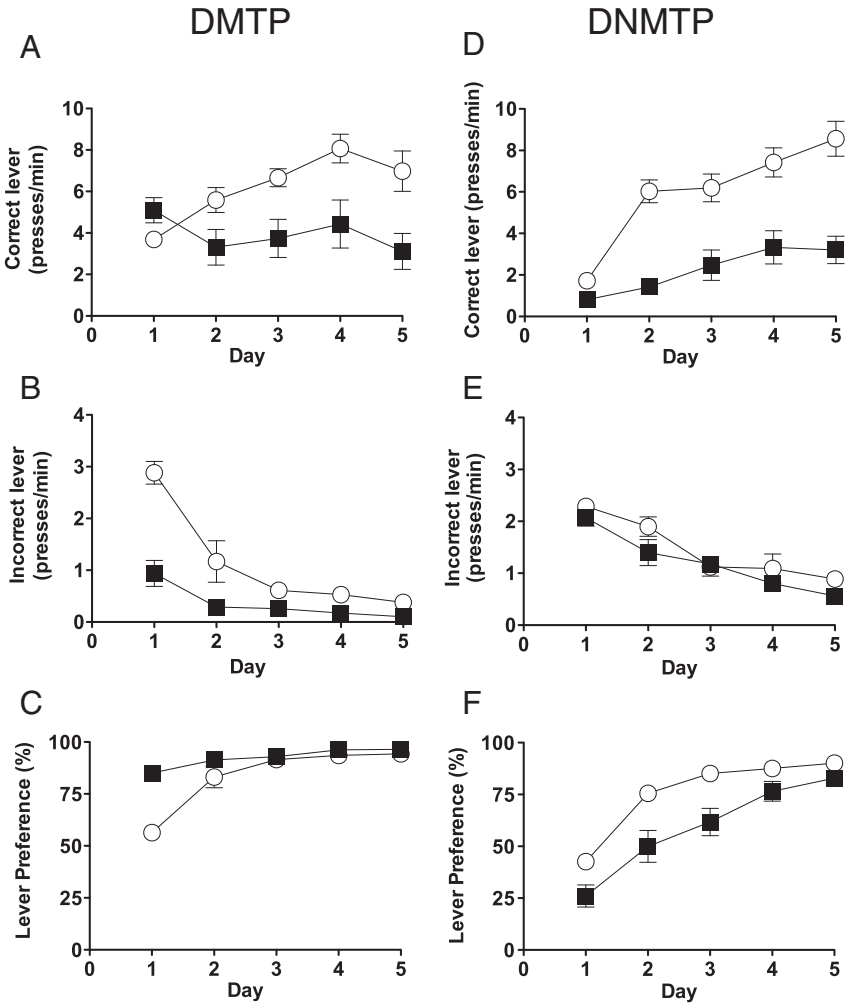

Fig. 6. Operant behaviour during the restoration phase of the experiment. The HF diet was removed at the end of week 5 and the SC diet was reinstated. The animals were re-tested on the operant DMTP for 5 days during week 10 and then switched to DNMTP paradigm and re-tested for a further 5 days during week 11. The data are presented as means ± SEM ($n = 8$ for each group). The open circles show the results for the SC-fed rats; the closed circles show the results for the HF-SC restored rats. Panels A and D show the mean pressing rate on the correct (rewarded) lever; panels B and E show the mean pressing rate on the incorrect (non-rewarded) lever; panels C and F show the mean preference for the reward lever.

4. Discussion

The principal finding of the current study is that feeding rats an HF diet for only 2 to 3 weeks elicited impairments in operant behaviour in a DMTP/DNMTP operant task that resemble those seen in rats treated with the diet for a longer period of time. Specifically, the animals were able to recall the DMTP task, learned prior to HF feeding, but showed impaired acquisition of the DNMTP task when the schedule was switched to this contingency. These impairments, however, are perhaps of a lesser degree than those reported in our previous study in which the rats were fed with the HF diet for 10–11 weeks before operant testing [8]. When the HF-fed rats were re-tested, after being returned to the control SC diet for 5 weeks following a period of HF feeding, some differences in behaviour were still observed. However, the deficit in responding in the DNMTP task was substantially ameliorated and the HF-SC restored group were able to acquire the DNMTP task effectively when assessed as the percentage of lever-pressing responses on the correct lever and the number of rewards gained. Feeding the HF diet, used in our laboratory, for 12 weeks elicits peripheral insulin resistance [8]. The current studies have shown that 4 weeks of HF feeding, using the regime employed in our laboratory, was also sufficient to evoke insulin resistance. When the animals were returned to the control SC diet after exposure the HF diet, these metabolic measures were comparable to the animals that had never been exposed to the HF diet. The data seem consistent with the possibility that these metabolic consequences of HF feeding may be implicated in the behavioural deficit observed. However, another study in our laboratory has shown that, while the administration of the *anti*-diabetic drug metformin attenuates the effects of an HF diet on body weight and insulin resistance, the drug has no significant effects on the impaired performance of HF-fed animals in the DMTP/DNMTP task [9]. Thus, its seems reasonable to conclude that increased peripheral insulin resistance *per se* is unlikely to explain the deficit in operant behaviour reported here.

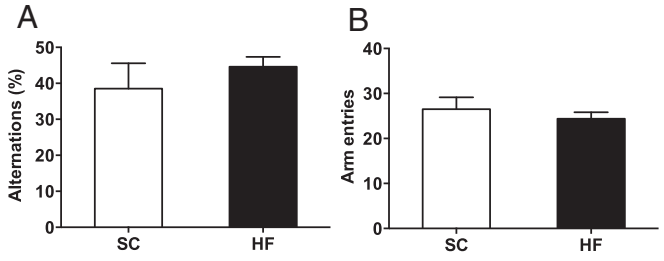

Fig. 7. Effect of diet on spontaneous alternation. Spontaneous alternation was assessed in a closed 4-arm maze in an open field. Animals were tested during week 4 week on the SC or HF diet for 10 min and percentage spontaneous alternations (A) and total arm entries (B) measured. The data are presented as means ± SEM (n = 8 for each group). p = ns SC vs HF.

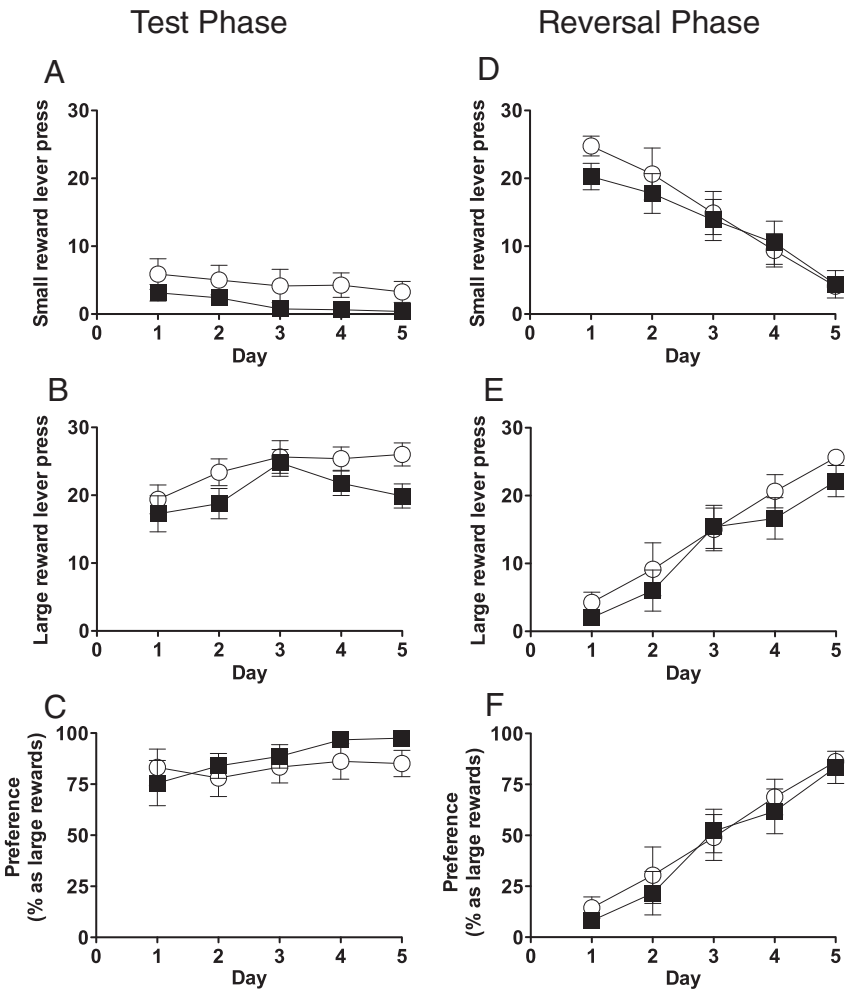

Fig. 8. Effect of diet on an operant reward preference task. Animals were tested during weeks 3 and 4 on the SC or HF diet. The data are presented as means ± SEM (n = 8 for each group). During week 3 (Test Phase) the reward value of the levers was the same as that used during training. Total responses on the levers delivering the smaller and larger rewards are presented in panels A and B respectively and were used to calculate the mean percentage of responses on the more highly rewarded lever (panel C). After 5 days of testing the reward value of the levers was reversed (Reversal Phase) and the mean responses on the levers which now delivered the small (panel D) and large rewards (panel E) were recorded and used to calculate preference for the larger reward (panel F). The open circles show the results for the SC-fed rats; the closed circles show the results for the HF-fed rats. p = ns SC vs HF.

Studies in other laboratories have shown that feeding rats diets rich in saturated fat impairs spatial and working memory in both water-maze and radial tasks [14]. While a majority of the studies employ long term exposure to high energy diets, there is some evidence that deficits in spatial working memory can develop after only 3 days of exposure to this type of diet [15]. Thus, it is possible that the deficits in operant responding seen in the current study could also reflect impairments of this nature. However, consumption of the diet employed in the current study did not result in impaired performance of the spontaneous alternation task, a task that detects impairments of spatial working memory [13,16,17]. Moreover, spatial learning in an open field water-maze task is also unaffected by long-term exposure to the diet employed in the current study [8]. Therefore, it seems reasonable to conclude that the deficit observed in the HF-fed rats in the current study is unlikely to reflect impaired spatial working memory.

The animals fed the HF diet made fewer lever-pressing responses on the rewarded lever when tested in the operant experiments. It is reasonable to suggest, therefore, that this explains the deficit in the acquisition of DNMTP contingency seen in the HF-fed animals. The reduction in the lever-pressing rate is unlikely to be the result of a generalised reduction in activity since the HF-fed rats were not less active than their SC-counterparts in either the 4-arm maze or the activity box. A more plausible explanation is that the reduced lever pressing may reflect reduced motivation to respond for the palatable reward used as a reinforcer in these experiments. La Fleur and colleagues [18] noted that increased satiety signals may limit responding for a palatable reward in an operant schedule and this effect may be exacerbated in rats fed an HF diet. Other studies have reported inconsistent effects of HF diets on food-motivated responding, the effects being influenced by factors such as the duration and nature of exposure to the diet and its composition [18–20]. Davis and colleagues [21] reported that 9 weeks of HF feeding attenuated responding for a sucrose reward in both a fixed ratio 1 and progressive ratio paradigms. These authors argued that the effect reflected a reduction in the motivation to respond for the reward and that this was mediated by the diminished dopamine (DA) turnover in the nucleus accumbens evoked by the diet. A subsequent microdialysis study [22] showed that long-term HF feeding diminished basal extracellular levels of DA in nucleus accumbens and attenuated the increase evoked by an injection of amphetamine. It may be significant that both short-term (this study) and long-term [8] exposure to the HF diet employed in the current studies elicits a substantial increase in plasma leptin since the administration of this hormone has been shown to reduce basal and feeding evoked DA overflow in the nucleus accumbens [23] and the motivation to respond for a palatable reward [24]. The effect seems to be mediated by leptin receptors in the hypothalamus that restrain over-consumption of calorically dense foods and the midbrain that regulate effort-based responding for palatable food rewards [25]. The hypothesis is supported

by the evidence from a previous study that the co-administration of the *anti*-diabetes drug, metformin, fails to ameliorate the reductions in response rate and lever selection accuracy observed in the DMTP/DNMTP task observed in HF-fed rats [9]. Metformin administration reversed the effects of HF feeding on weight gain and peripheral insulin resistance but had less effect of the raised plasma leptin concentrations seen in the HF-fed animals.

While the data provided support for the hypothesis that HF feeding diminishes the motivation to respond for a palatable reward, it is important to note that other results do not seem to be consistent with this conclusion. The results of the operant study in experiment 3 suggest that HF-fed rats do not differ in their responses for a sucrose reward and retain the ability to adapt their responding in a simple operant task differentially reinforced with a large and small reward when the contingency is changed. This observation could reflect responding to a task that is less demanding than the DMTP/DNMTP task or that the larger reward used in the task overcomes the motivational deficit evoked by HF feeding. Indeed, the study by Geiger and colleagues [22] demonstrated that, although feeding an HF diet blunted the mesolimbic DA response to a moderate reward, increasing the incentive value of the reward could surmount this effect. These authors argued that this mechanism may drive the compulsion for obese individuals to seek highly palatable foods.

By test day 2 of the restoration phase of experiment 1 the performance of the SC control rats matched the optimum performance achieved by this group during the first (diet) phase of the experiment. These results suggest that the animals recalled their previous experience of both contingencies. Similarly, in the DMTP contingency, the performance of the HF-SC group of animals was similar to that of the rats tested while still on the HF diet. When tested on the DNMTP contingency, the HF-SC animals pressed at a higher rate on the rewarded lever, exhibited a greater preference for the correct lever and gained substantially more rewards than they had when tested during the diet phase of the experiment. These results imply that HF-SC animals exhibited a greater degree of behavioural flexibility in the task than that demonstrated by the same rats when tested during the diet phase of the study. The rate of lever pressing on the correct lever, however, exhibited by the HF-SC restored animals during the restoration phase remained significantly below that of the rats fed the SC diet throughout in both the DMTP and DNMTP contingencies. This effect cannot be explained by differences in the plasma leptin levels between the two groups. Higher lever pressing rates for a sucrose pellet have been taken as evidence of increased motivation to respond for a reward [26]. Thus, these data could imply that feeding an HF diet for even a short period of time may elicit impairments of reward motivation which persist for some weeks after returning to a balanced low fat diet. This possibility merits further investigation.

In conclusion the findings suggest that the ingestion of diets rich in saturated fat for a relatively short period of time is sufficient to induce harmful metabolic changes that presage type 2 diabetes and persistent motivational changes that may impair the ability to modify food-reinforced behaviour. The motivational deficit, if replicated in humans, may make subjects more resistant to the dietary changes required to improve health, especially if this involves switching to a diet in which the incentive value of components such as saturated fat and sucrose are substantially reduced.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.physbeh.2016.08.035.

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