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High fat diet increases the incidence of orofacial dyskinesia and oxidative stress in specific brain regions of rats

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Abstract

Haloperidol-induced orofacial dyskinesia (OD) is a putative animal model of tardive dyskinesia (TD) whose pathophysiology has been related to free radical generation and oxidative stress. Schizophrenic patients have been reported to eat a diet higher in fat than the general population and dietary fat intake can lead to an increase in oxidative stress in animal models. The objective of this study was to determine whether association of ingestion of a high fat diet with prolonged haloperidol treatment could lead to OD and oxidative stress in the rat brain. Haloperidol decanoate administration (38 mg/kg, IM, which is equivalent to 1 mg/kg/day) monthly for a period of 6 months to rats fed previously with a high fat and normo fat diets (6 months) caused a increase in vacuous chewing (VCM) and duration of facial twitching (FT). Haloperidol caused a reduction in body weight gain and the loss of body weight occurred after 4 months of treatment with haloperidol. The effects on body weight were more accentuated in HF diet group. HF diet ingestion was associated with an increase in TBARS levels in cerebellum and cerebral cortex (regardless of haloperidol treatment). A significant diet × haloperidol treatment interaction in striatum, subcortical parts and the region containing the substantia nigra was observed for TBARS. In fact, haloperidol caused an increase in TBARS levels of these regions only in rats fed with the HF. These results indicate that a high fat diet caused a transitory increase in haloperidol-induced OD in rats and this in part can be related to the haloperidol-induced oxidative stress in brain structures involved with OD.

Keywords: Haloperidol; Orofacial dyskinesia; Tardive dyskinesia; Free radical; Neuroleptics; Neurotoxicity; High fat diet

1. Introduction

Schizophrenia is the major mental disorder that has a lifetime risk of 1% and affects at young age in many cultures around the world (Mahadik et al., 2001). Haloperidol, a typical member of the conventional neuroleptics, is thought to exert its motor side effects through striatal dopamine D_2-receptors (Creese et al., 1976) and sigma-receptors (Walker et al., 1990; Vilner et al., 1995). The neuroleptic efficacy of haloperidol in psychotic patients is somewhat compromised by the drug's liability to cause acute and chronic extrapyramidal side effects, including TD (Andreasen and Jorgensen, 2000). The mean prevalence of TD is 20–25% in subjects receiving classical neuroleptic treatment, but the rate increases strongly with age, and prevalence above 50% has been reported in patients older than 50 years (Kane and Smith, 1982; Woerner et al., 1991; Yassa and Jeste, 1992). The most serious aspect of TD is that it may persist for months or years after drug withdrawal, and in some patients it is irreversible (Crane, 1973; Jeste et al., 1979; Casey, 1985). Some neurochemical hypothesis has been proposed for the development of TD during the last decades. They include dopaminergic hypersensitivity, disturbed balance between dopaminergic and cholinergic systems, dysfunction of striatonigral GABAergic neurons and excitotoxicity (Andreasen and Jorgensen, 2000; Ebadi and Srinivasan, 1995). However, the molecular mechanisms

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responsible for the neuropathophysiology of TD are still not completely understood.

One hypothesis that has gained experimental support in literature is that free radicals may play an important role in the physiopathology of such disorders (Cadet et al., 1986, 1987). In line with this, literature of data indicates that neuroleptic administration can increase the turnover of dopamine and the production of reactive substances as products of dopamine metabolism (Andreasen and Jorgensen, 2000; Casey, 1995; Lohr, 1991; Polydoro et al., 2004). Furthermore, blockage of striatal dopamine receptors can produce an increase in extracellular glutamate (Burger et al., 2005; See and Lynch, 1996), which in turn can increase the production of free radical species (Castilho et al., 1999; Coyle and Puttfarcken, 1993; Tsai et al., 1998).

In line with this hypothesis, several authors have demonstrated the reversion of OD with the administration of antioxidants substances, including FK-506 (Singh et al., 2003), melatonin (Naidu et al., 2003a,b), quercetin (Naidu et al., 2003a,b), ebselen (Burger et al., 2003) and diphenyl–diselenide (Burger et al., 2004). Recently, Abílio et al. (2004) reported that striatal catalase has an important role in the protection of spontaneously hypertensive rats (SHR) against the reserpine-induced OD. Most importantly, patients with TD have elevated markers of oxidative stress in CSF and plasma when compared to controls subjects (Lohr et al., 1990; Tsai and Ikonomidou, 1995; Brown et al., 1998). Additionally some authors have demonstrated that high doses of vitamin E are able to prevent TD in patients under chronic with neuroleptic treatment (Egan et al., 1992; Adler et al., 1993).

Dietary fat intake has been shown to be important in the development of human obesity (Warwick and Schiffman, 1992) and there are also experimental studies showing that high fat diet can be associated with increased oxidative stress in rodents (Storlien et al., 1986, 2000; Folmer et al., 2003) and more recently literature data have indicate that high fat diet may increase the vulnerability of dopaminergic neurons to MPTP (Choi et al., 2005).

Of particular importance, schizophrenic patients have been reported to eat a diet higher in fat than the general population (Brown et al., 1999) and Gardos and Cole (1986) suggested that schizophrenia may confer resistance to the development of tardive dyskinesia. However, there are no data in the literature indicating that excessive fat intake can change the incidence of tardive dyskinesia in schizophrenics. High level of fat intake is considered to be an important factor in the development of insulin resistance and obesity. Schizophrenic individuals appear to have at increased risk for certain obesity-related conditions such as type II diabetes and cardiovascular disease (Mukherjee et al., 1996) in comparison with general population. Metabolic dysfunctions have been associated with antipsychotic treatment including increased levels of circulating leptin and these changes can be an important link in the development of overweight and the insulin resistance syndrome in subjects receiving antipsychotic drugs (Hagg et al., 2001; Haupt et al., 2005; Henderson, 2002; Kraus et al., 1999; Melkersson et al., 2000; Morimoto et al., 1999; Simpson et al., 2001).

In line with this, over production of reactive oxygen species (ROS) and antioxidant depletion have been associated with the diabetes manifestation (Hunt et al., 1988; Wolff and Dean, 1987), OD in animal models (Naidu et al., 2003a,b; Burger et al., 2003) and TD in humans (Andreasen and Jorgensen, 2000; Lohr et al., 2003). These considerations raise the possibility that a relation among neuroleptic treatment and diet can exist. Furthermore, it is plausible to suppose that some exacerbation of their pro-oxidant activity could occur by simultaneous exposure to them.

The aim of this study consisted in investigate the effects of the normo fat (NF) and high fat (HF) diets on the development of OD haloperidol-induced and TBARS in brain regions as measure of oxidative stress.

2. Materials and methods

2.1. Drugs

Haloperidol decanoate (Janssen Pharmaceutical); ketamine (Dopalen/ Division VetBrands/ Sespo-Brasil). Haloperidol was injected intramuscularly (I.M.) and Ketamine was injected intraperitoneally (i.p.).

2.2. Animals and diets

Male Wistar rats (2 months old), weighing between 270 and 320 g, from our own breeding colony (Animal Householding, UFSM, Brasil) were kept in wire cages with free access to the diets and water, in a room with controlled temperature (22±3 °C) and in 12-h light/dark cycle with lights on at 7:00 am. The animals were maintained and used in accordance to the guidelines of the Committee on Care and Use of Experimental Animal Resources, School of Veterinary Medicine and Animal Science of the University of São Paulo, Brasil.

The rats were randomly divided into two groups, with 16 animals each, and a fed either a NF or a HF diet. The composition of the diets is shown in Table 1. Food was placed daily before the beginning of the dark cycle. Food offering was adjusted in such a way that leftovers were less than 10%. Diets were prepared weekly and stored at 4 °C. Rats received the diets for 13 months and were monthly weighed.

2.3. Induction of orofacial dyskinesia

Chronic OD haloperidol-induced occurred after 6 months of the treatment with diets, when the rats were divided in two subgroups. The NF control group ($n=7$) received NF diet and vegetable oil solution intramuscularly (I.M.). The NF haloperidol group ($n=7$) received NF diet and haloper-

Table 1

Composition of the diets	High fat diet (HF)	Normo fat diet (NF)
	(g/kg)	
Protein	75.0	76.0
Carbohydrate	483.0	765.0
Fiber	35.00	37.00
Fat acid saturated	125.00	8.00
Fat acid unsaturated	230.0	62.0
Salt mixture[1]	48.00	48.00
Caloric content (cal/g)	5.35	3.91

[1]The salt mixture has the following composition (g/kg): KCl, 96.3; $MgSO_4$, 56.7; $ZnCl_2$, 0.4; $CuCO_4$, 0.7; $MnSO_4$, 1.2; bonemeal, 449; salt ligth, 152. The values were retired from Andriguetto (1986).

idol decanoate (I.M.), the HF control group ($n=7$) received HF diet and vegetal oil (I.M.) and the HF haloperidol ($n=9$) group received HF diet and haloperidol decanoate (I.M.). The haloperidol groups received the depot neuroleptic drug, haloperidol decanoate (Janssen Pharmaceutical) at a dose of 38 mg/kg, the equivalent of 1 mg/kg/day of unconjugated haloperidol. Injections were given intramuscularly each 4 weeks during one period of 7 months.

2.4. Behavioral testing

One behavioral analyze was realized in the beginning of treatment with the diets (0 month) and compared with 6 months of diet intake. Haloperidol treatment was started after 6 months of experimental diets intake. We examined the effect of haloperidol decanoate after 28 days (1 month) of the first injection, because it is well established in the literature that haloperidol-treated animals develop orofacial dyskinesia (Andreassen et al., 1998, 2003; Egan et al., 1999; Hamid et al., 1998). The others evaluations were performed 2, 3, 4, 5, 6, 7 months of haloperidol treatment. To quantify the occurrence of orofacial dyskinesia rats were placed individually in cages ($20\times20\times19$ cm) and hand operated counters were employed to vacuous chewing (VCMs) frequency and stopwatches were employed to score the duration of twitching of the facial musculature (FT).

VCMs are referred as a single mouth opening in the vertical plane not directed towards physical material. If VCMs or FT occurred during a period of grooming they were not taken into account. The behavioral parameters of orofacial dyskinesia were measured continuously for 6 min after a period of 2 min adaptation. During the observation sessions, mirrors were placed under the floor and behind the backwall of the experimental cage to permit observation when the animal was faced away from the observer. The behavioral tests were always conducted by four observers blind.

2.5. Experimental procedure

After 30 days of the last administration of drugs and 24 h of last section of behavioral quantification, all the rats were injected with the anesthetic ketamine (1 mg/kg) (Dopalen/ Division VetBrands/ Sespo-Brasil). After the rats were killed for decapitation, the brains were immediately excised and the cerebellum, cerebral cortex, striatum, region containing the substantia nigra and subcortical parts of the brain were separated, weighed and homogenized in 10 volumes (w/v) of 10 mM Tris–HCl, pH 7.5. The homogenates were centrifuged for 10 min at 1800 $\times g$ and the supernatant was used to TBARS determination as described early on (Ohkawa et al., 1979; Rossato et al., 2002).

2.6. Statistical analysis

Data were analyzed by a two- and three-way ANOVA, followed by Duncan's post hoc tests when appropriated. F values are presented in the text only the p value associated with it was <0.05. Significance was considered when $p<0.05$.

3. Results

Diet had no effect on body weight gain (Fig. 1). Two-way ANOVA (2 diets $\times$ 7 weight determinations) revealed no

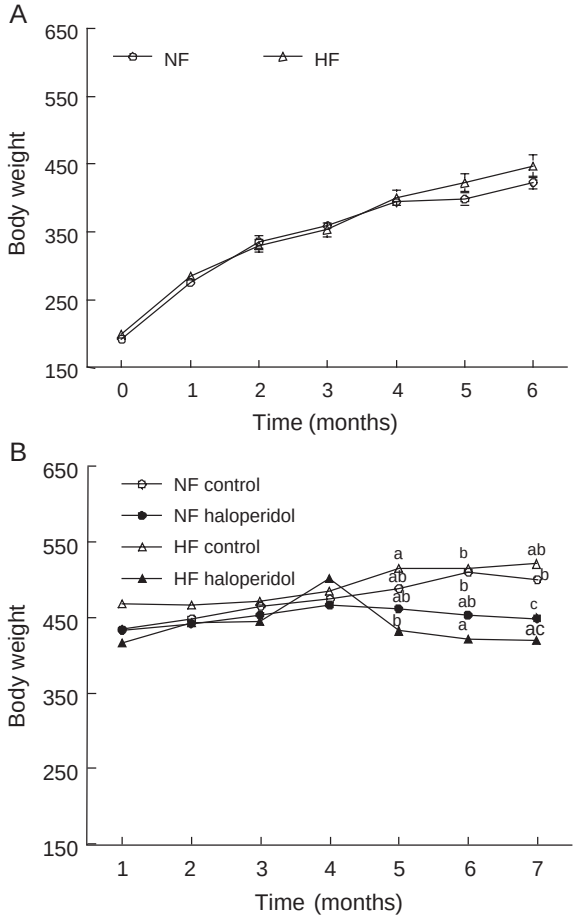

Fig. 1. A) Body weight in rats fed normo fat (NF) and high fat (HF) diets for 6 months. B) Body weight in rats receiving diets and haloperidol treatment. The symbols indicates a significant difference (detected by Duncan's multiple range test) between the groups into same month ($p<0.05$).

significant effects. Haloperidol treatment caused a significant reduction in body weight of rats in both dietary groups. However, rats from HF diet started to loss body weight before of the animals from NF diet. This was evidenced by a significant interaction between body weight and haloperidol treatment with $F(6, 150)=8.50$ and $p<0.001$.

Ingestion of the HF for 6 months caused an increase in the facial twitching frequency, when compared to rats fed with the diet containing normal fat (NF) content (Fig. 2; $p<0.01$). Main effect of haloperidol ($F(1,28)=25$).

Haloperidol caused a marked increase on VCM. However, the effect of haloperidol varied depending on the dietary treatment. In fact, rats on HF diet treated with haloperidol displayed an increase in VCM from the 3rd to the 5th month of treatment, when compared to animals from NF diet. This was evidenced by a significant third order interaction (diet × haloperidol × months) with $F(6,138)=6.33$ and $p<0.001$.

Haloperidol caused a marked increase on FT. However, the effect of haloperidol varied depending on the dietary treatment. In fact, rats on HF diet treated with haloperidol displayed an increase in FT from the 4th to the 6th month of treatment, when compared to animals from NF diet. This was evidenced by a significant interaction between haloperidol × months with $F(1,26)=74.56$ and $p<0.001$ (Fig. 3).

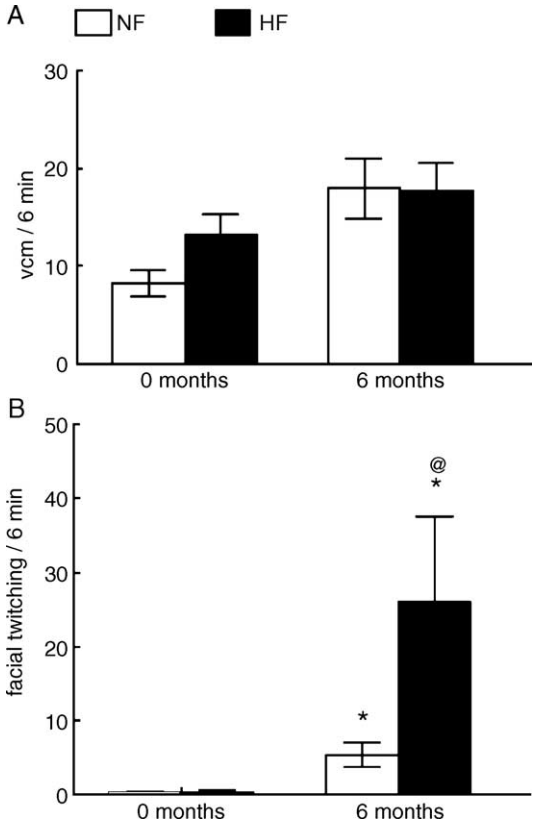

Fig. 2. Effects of the diet on orofacial dyskinesia. Vacuous chewing movements (A) and facial twitching (B) frequency in 6 min in the beginning of treatment (0 months) and after 6 months of treatment with the NF and HF diet. The values are indicated as mean±S.E.M. @Indicates a significant difference between the groups ($p<0.05$) and *indicates a significant difference into the same diet in relation to the beginning of treatment by ANOVA.

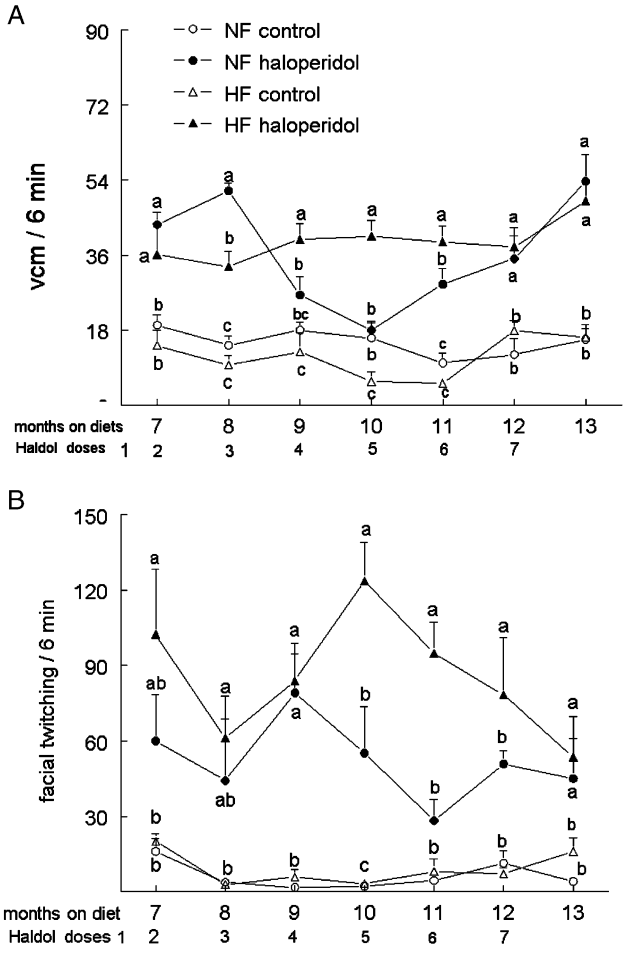

Fig. 3. Effects of haloperidol (1 mg/kg/day) or vehicle (vegetable oil) long-term administration on vacuous chewing movements (A) and facial twitching (B) frequency concomitant of treatment with NF and HF diet. Values are express as means. Symbols indicates a significant difference between means of groups ($p<0.05$) in the same behavioral session. Two-way ANOVA following by Duncan's tests.

Two-way ANOVA of cortical TBARS levels revealed a significant main effect of diet ($F(1,26)=7.73$ and $p<0.01$), indicating that HF increased oxidative stress in this region. In fact, the levels of TBARS in HF group (575.8±40.2) was significantly higher than that of NF group (442.3±13.2). However, post hoc comparisons by Duncan's multiple range test indicated a significant difference only between rats treated with haloperidol. Two-way ANOVA of striatal TBARS levels revealed a significant interaction of diet and haloperidol ($F(1,26)=6.6$ and $p<0.05$), indicating that HF associated with haloperidol administration increased oxidative stress in this region (Fig. 4).

Post hoc comparisons by Duncan's multiple range test indicated a significant difference in the group HF treated haloperidol than others groups. Two-way ANOVA of subcortical TBARS levels revealed a significant interaction of diet and haloperidol ($F(1,26)=8.94$ and $p<0.01$), indicating that HF ingestion associated with haloperidol administration increased oxidative stress in this region of the brain. Two-way ANOVA of TBARS levels of the

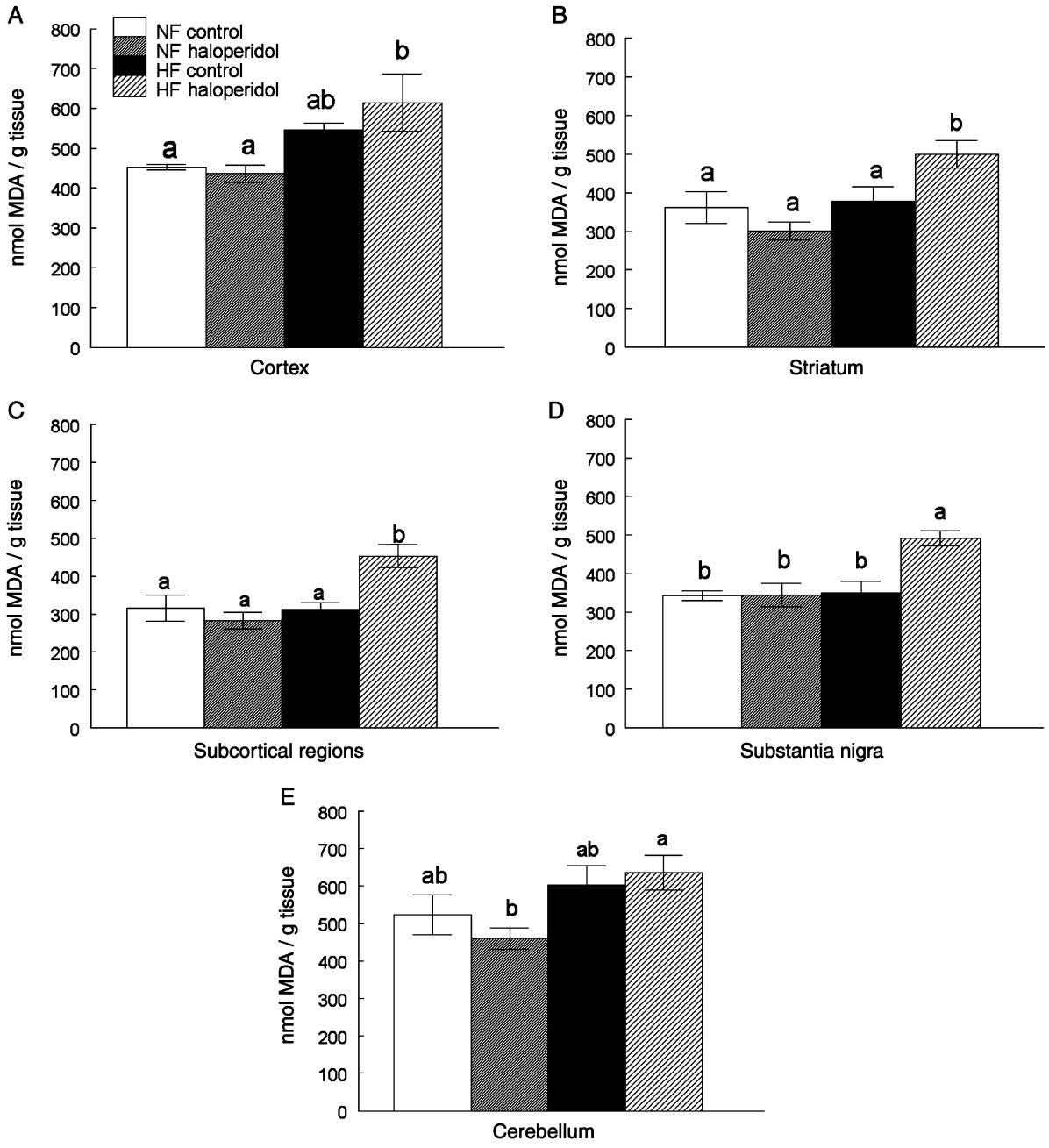

Fig. 4. Thiobarbituric acid-reactive species (TBARS) concentrations in cerebral cortex (A), striatum (B), subcortical parts (C), region of substantia nigra (D) and cerebellum (E) in rats after 13 months in a NF or HF diet and after treatment with haloperidol for 7 months. Values are means ± S.E.M. Symbols represent significant differences between the groups ($p < 0.05$). Two-way ANOVA followed by Duncan's multiple range tests.

region containing the substantia nigra revealed a significant interaction of diet and haloperidol ($F(1,26) = 9.72$ and $p < 0.01$), indicating that HF increased oxidative stress in this region. Two-way ANOVA of TBARS levels of cerebellum revealed a significant main effect of diet ($F(1,26) = 3.27$ and $p < 0.01$), indicating that HF increased oxidative stress in this region of brain. In fact, TBARS levels in cerebellum of rats fed the HF (608.4 ± 33.6) were significantly higher than that detected in cerebellum of rats raised on NF (493.3 ± 31.7). However, post hoc comparisons by Duncan's multiple range test indicated a significant difference only between rats treated with haloperidol.

4. Discussion

The results of the present study indicate that the high fat diet caused an increase in the incidence of OD in rats. However, this effect was transitory and disappeared one month latter. Additionally, we observed that a concomitant ingestion of the high fat diet with haloperidol administration

resulted in an increase in OD in rats. This effect was also transitory and disappeared when the treatment with haloperidol continued. For the case of VCM, the disappearance resulted from an increase in the OD of rats maintained in the normal diet. For the case of facial twitching, the disappearance was a consequence of a more complex change in OD in both groups. One factor that could contribute to modify the level of FT is the reduction in food intake after prolonged haloperidol administration. In fact, the haloperidol effects are complicated by the fact that the treatments caused a relative loss in body weight which was most exaggerated in the haloperidol plus high fat diet group. The uncontrolled effect of bodyweight loss could in part explain some of the variations listed above. This hypothesis, although tentative, is in accordance with expanding literature data indicating that food restriction reduces the production of oxidative stress in mammals (Armeni et al., 2003) and can also release neurotrophic factors (Mattson, 2000). These results indicate that the two behavioral measures did not necessarily reflect the same pathophysiological effect of neuroleptics and indicate that they can be independently modulated by exogenous factors, including aging and food ingestion. In line with this, in a previous study we observed that ebselen (Burger et al., 2003), an antioxidant agent, affected in different ways these behavioral measures in rats exposed to reserpine.

Literature data indicates that exposure to haloperidol causes an increase in cerebral oxidative stress (Andreasen and Jorgensen, 2000; Casey, 1995; Lohr, 1991; Clow et al., 1980; Slivka and Cohen, 1985; Tse et al., 1976; Abílio et al., 2002, 2003) that may be causally linked to an increase in orofacial dyskinesia after neuroleptic treatment. The results of the present investigation indicated that long-term consumption of the high fat diet caused an increase in oxidative stress in cerebral cortex and cerebellum, as indicated by a significant effect of diet regardless of the haloperidol treatment. Of particular importance for OD, haloperidol caused an increase in TBARS production in the high fat diet group specifically in the regions of the brain that are thought to be involved in the genesis of tardive dyskinesia (Lohr et al., 2003; Tsai and Ikonomidou, 1995), i.e., striatum and the region containing the substantia nigra. However, the increase in TBARS production in these regions cannot exclusively account for the increase in the OD, because there were no significant differences in the OD parameters between the two dietary groups treated with haloperidol in the end of the observation period.

Taken together the results of the present investigation indicate that high fat diets ingestion for a long period can have some transitory behavioral effects on rats. Furthermore, here we demonstrated for the first time that simultaneous ingestion of high fat diet and chronic haloperidol administration caused transitory exacerbation of orofacial dyskinesia in rats, however the animal model cannot to reflect the same effects in humans. Although literature data indicate that neuroleptic-induced orofacial dyskinesia is associated with oxidative stress, here we are unable to establish such correlation, because haloperidol increased the brain oxidative stress only in rats maintained on a high fat diet and the incidence of OD was similar between the high fat and normal fat diets groups. One explanation to these finds may reside on an anticipation of oxidative stress in high fat diet fed rats treated with haloperidol that is previous to development of OD in rats. This is agreement with Andreassen et al. (1998) and Calvent et al. (2002) where the nitropropionic acid administration can potentiate the orofacial dyskinesia of rats. The disappearance of differences between NF and HF diet groups may be a consequence of a complex interaction with other factors that affect OD in rodents, particularly the age of the animals (Kane and Smith, 1982; Woerner et al., 1991; Yassa and Jeste, 1992) or others compensatory mechanisms such as neurotransmission plasticity that could follow the neuronal consequences of oxidative stress and could also be influenced by aging.

5. Conclusion

In conclusion, the results of the present investigation demonstrated that high fat diet ingestion can enhance the OD produced by a typical neuroleptic used for the treatment of schizophrenia. It is known that schizophrenic patients eat more fat than the general population (Brown et al., 1999); however, there are no data in the literature indicating that the incidence of TD is more frequent in those schizophrenic patients eating diets with high content of fat.

Although it is still premature to extrapolate the relevance of our findings to man, we realize that epidemiological studies should be carried out to determine a possible increase in the incidence of TD in patients fed with more fatty diets. However, we must emphasize that the animal model used here did not replicate the situation found in humans. In fact, the chronic use of haloperidol and others neuroleptics are frequently associated with obesity in schizophrenic patients and in our rat model haloperidol cause loss of weight.

In spite of this, haloperidol-treated rats showed OD, indicating that in rats obesity is not a mandatory factor for the development of OD.

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