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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-