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Possible beneficial effect of peroxisome proliferator-activated receptor (PPAR) — α and γ agonist against a rat model of oral dyskinesia

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ABSTRACT

Tardive dyskinesia is a type of hyperkinetic movement disorder which consists of abnormal involuntary movements, characterized by orofacial movements. Previous studies suggest that oxidative stress and neuroinflammation play important role in the pathogenesis of TD. Recently, PPAR-α and PPAR-ϒ have been reported as neuroprotective agent in various animal models. The present study investigated the neuroprotective effect of PPAR-ϒ agonist, pioglitazone (20 and 40 mg/kg, p.o.) and PPAR-α agonist, fenofibrate (100 and 200 mg/kg, p.o.) in an animal model of oral dyskinesia.

Oral dyskinesia was induced by chronic administration of haloperidol (1 mg/kg i.p.) for 21 days. Chronic administration of haloperidol significantly increased vacuous chewing movements, tongue protrusions, facial jerking, sniffing and grooming in rats which was dose-dependently inhibited by pioglitazone and fenofibrate. Further, it also decreased % retention of memory in an elevated plus maze test on day 22. Chronic administration of haloperidol also induced oxidative damage and neuroinflammation (TNF-α and IL-1β) in brain regions. The fenofibrate and pioglitazone were able to reverse the behavioral and biochemical changes induced by haloperidol. Further the study proposed the antioxidant and antiinflammatory effects of both PPAR agonists in this model. We concluded that administration of pioglitazone and fenofibrate individually or in combination along with antipsychotic in the treatment of schizophrenia, prevent or delay the symptoms of oral dyskinesia.

1. Introduction

Tardive dyskinesia (TD) is known as iatrogenic (drug-induced) (Aia and Revuelta, 2011) hyperkinetic movement disorder which consists of choriform, athetoid and rhythmic abnormal involuntary movements (Kulkarni and Dhir, 2011). Orofacial movements such as vacuous chewing movements (VCMs), facial jerking, grimacing, tongue protrusion, lip smacking are the main features of TD. TD appears months or years after the initiation of antipsychotic treatment and it may persist even after drug withdrawal and may be irreversible in 20% of schizophrenic patient (Latha et al., 2010). Haloperidol and other antipsychotics are used for the treatment of schizophrenia. Most of the antipsychotic especially typical antipsychotics block dopamine receptors, and their toxicity occurs due to the generation of free radicals and increased lipid peroxidation which may be the result of concomitant increase in turnover of this amine (Bishnoi et al., 2007).

Although the hypothesis of dopamine supersensitivity plays a major role in the pathophysiology of TD, the long term use of these antipsychotic also cause GABA insufficiency (Samad et al., 2008), serotonin receptor dysfunction (Kulkarni et al., 2009), glutamate receptor dysfunction (Kulkarni et al., 2009), oxidative stress (Kulkarni and Naidu, 2003; Thaakur and Himabindhu, 2009) and neuroinflammation (Bishnoi et al., 2008a,b). Based on these reports TD pathogenesis involves multiple pathways including neurotransmitters disbalance, oxidative stress and neuroinflammation.

PPARs are the transcription factors belonging to the superfamily of nuclear receptors (Heneka and Landreth, 2007). Activation of the PPAR-γ and PPAR-α subtype are known to increase insulin sensitization, modulate glucose and lipid metabolism, respectively (Swanson et al., 2011; Bhateja et al., 2012). Pioglitazone is a thiazoledinedione (TZD) and a highly selective PPAR-γ agonist (Swanson et al., 2011). Fenofibrate is a highly selective agonist of PPAR-α (Bhateja et al., 2012). Various reports suggests that pioglitazone (a PPARϒ agonist) and fenofibrate (a PPAR α agonist) have neuro-protective role in various diseases like PD (Carroll et al., 2012; Xiang et al., 2012; Kreisler et al., 2010), traumatic brain injury (Besson et al., 2005; Thal et al., 2011), Alzheimer's disease (AD) (Dhikav and Anand, 2011), Cerebral ischemia (Medhi et al., 2010), HD (Kalonia et al., 2010; Bhateja et al., 2012) and ALS (Kiaei, 2008).

The aim of this study was to investigate a possible beneficial effects of P PPAR-γ and PPAR-α agonists on the behavioral (oral dyskinesia, motor activity and memory) and neurochemical (oxidative stress and neuroinflammation) changes induced by long-term treatment with haloperidol in rats.

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2. Materials and methods

2.1. Animals

Male Wistar rats, weighing 180–250 g (3–5 month old), were obtained from Central Animal House facility of I.S.F. College of Pharmacy, Moga, Punjab, India. Animals were housed in group of three, in polypropylene cages with husk bedding under standard conditions of light and dark cycle with food and water *ad libitum*. Animals were acclimatized to laboratory conditions before the test. All the behavioral assessments were carried between 9: 00 and 17: 00 h. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and was carried out in accordance with the guidelines of the Indian National Science Academy (INSA) for the use and care of the experimental animals. All the experiments for a given treatment were performed using age-matched animals in an attempt to avoid variability between experimental groups.

2.2. Drugs and treatment schedule

The drugs used in the present study were: haloperidol (Intas Pharmaceuticals ltd., Matoda, Ahmadabad, India) was dissolved in distilled water. Pioglitazone, (PPAR-ϒ agonist) was obtained as a gift sample by Ind-Swift Laboratories ltd., Baddi, Himachal Pradesh, India. PPARα agonist i.e. fenofibrate was obtained as ex-gratia sample from Biocon ltd., Bangalore and Trichem Life Sciences ltd., Tarapur, Palghar, Maharashtra. Pioglitazone and fenofibrate were suspended in 1% and 0.5% Carboxy methyl cellulose (CMC), respectively (Pathan et al., 2006; Oliveira et al., 2007) and the suspensions were freshly prepared. The Pioglitazone was administered at doses of 20 and 40 mg/kg orally (Kalonia et al., 2010). Fenofibrate was administered at doses of 100 and 200 mg/kg orally (Bhateja et al., 2012). The doses were selected on the basis of previous published data related to their neuroprotective effects.

Group I — Vehicle treated (saline i.p + CMC p.o)
Group II — Haloperidol (1 mg/kg i.p.) + CMC p.o
Groups III and IV — Haloperidol (1 mg/kg i.p.) + Pioglitazone (20 and 40 mg/kg p.o.)
Groups V and VI — Haloperidol (1 mg/kg i.p.) + Fenofibrate (100 and 200 mg/kg p.o.)
Group VII — Haloperidol + Pioglitazone (20 mg/kg p.o.) + Fenofibrate (100 mg/kg p.o.)
Group VIII — (Saline i.p + Pioglitazone 40 mg/kg p.o.) *perse*
Group IX — (Saline i.p + Fenofibrate 200 mg/kg p.o.) *perse*

Haloperidol was administered i.p. in a volume of 1 ml per 200 g of body weight. Pioglitazone and fenofibrate were administered orally in a constant volume of 0.5 ml per 100 g of body weight of rat once daily for 21 days. The Pioglitazone and fenofibrate administered 30 min before the haloperidol treatment. All the groups receive equal number of injections.

All the behavioral parameters were observed before treatment on day 0, 7, 14 and 22 of haloperidol treatment. Behavioral parameters were observed in sequence on each day starting with locomotor at 9:30 AM then rotarod activity (11:00 AM) followed by VCMs, tongue protrusion, facial jerking and sniffing and grooming in each animal. Treatments were given in all the groups in the evening after behavioral observation on respective day.

2.3. Induction of orofacial dyskinesia

Orofacial dyskinesia was induced by the chronic administration of haloperidol (1 mg/kg i.p.) to rats for a period of 21 days. All the behavioral parameters were assessed every week (i.e. on day 0, 7, 14) and last behavioral assessment was done 24 h after the last dose of haloperidol i.e. on day 22nd (Bishnoi et al., 2008a,b).

2.4. Measurement of body weight

Animal body weight was recorded on the first and last day of experimentation. Percent change in body weight was calculated as:

$$\frac{\text{Body weight (day 1)} - \text{Body weight (day 22)} \times 100}{\text{Body weight (day 1)}}$$

2.5. Assessment of behavioral parameters

2.5.1. Assessment of orofacial movements

On the test day, the rats were placed individually in plexiglass (30 × 20 × 30 cm) cage for the assessment of oral dyskinesia. Animals were allowed 10 min to get used to the observation cage before behavioral assessments. To quantify the occurrence of oral dyskinesia, hand-operated counters were employed to score vacuous chewing, tongue protrusion, facial jerking and sniffing and grooming frequencies. In the present study, VCMs are referred to as single mouth opening in the vertical plane not directed towards physical material. If tongue protrusion or VCMs occurred during a period of grooming, they were not taken into account. Counting was stopped whenever the rat began grooming, and restarted when grooming stopped. Mirrors were placed under the floor and behind the back wall of the cage to permit observation of oral dyskinesia when the animal was faced away from the observer. The behavioral parameters of oral dyskinesia were measured continuously for a period of 10 min. In all the experiments, the scorer was unaware of the treatment given to the animals (Bishnoi et al., 2007, 2008a, b, 2009).

2.5.2. Rota-rod activity

Motor coordination was assessed for all rats on a rotarod. Rats were placed individually on a rotating rod with a rod of 7 cm (speed 25 rpm). Prior to any treatment, rats were trained in a single session until they attained 150 s on rotarod (Samad et al., 2008). Then fall off time was recorded during drug treatment every week (Kumar and Kumar, 2009).

2.5.3. Total locomotor activity

The locomotor activity was monitored using an activity meter (Medicraft, INCO, Ambala, Haryana, India). Before subjecting the animal to cognitive task, they were individually placed in the activity meter and the total activity count was registered for 10 min. The locomotor activity was expressed in terms of total photo beam interruption counts/10 min per animal (Bishnoi et al., 2007; Kumar et al., 2011a,b).

2.5.4. Elevated plus maze test

The elevated plus maze was used to evaluate spatial long-term memory. Briefly, the apparatus consisted of two open arms and two closed arms. The arms extended from a central platform, and the maze was elevated to a height of 50 cm from the floor. On the first day, each animal was placed at the end of an open arm. Transfer latency (TL), that is the time taken by the rat to move into one of the closed arm, was recorded on the first day. If the animal did not enter into a closed arm within 90 s it was gently pushed into one of closed arms and the TL latency was assigned as 90 s. The rat was allowed to explore the maze for 20 s and then was returned to the home cage. The rat was again placed in the maze next day (24 h later) and TL was recorded (Bishnoi et al., 2007; Kumar and Kumar, 2008). Percent retention was calculated by the formula:

$$\text{Transfer Latency (Day 1)} - \text{Transfer Latency (Day 2)} / \text{Transfer Latency(Day 2)} \times 100$$