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Beneficial effects of lycopene against haloperidol induced orofacial dyskinesia in rats: Possible neurotransmitters and neuroinflammation modulation

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ABSTRACT

Tardive Dyskinesia is a severe side effect of chronic neuroleptic treatment consisting of abnormal involuntary movements, characterized by orofacial dyskinesia. The study was designed to investigate the protective effect of lycopene against haloperidol induced orofacial dyskinesia possibly by neurochemical and neuroinflammatory modulation in rats. Rats were administered with haloperidol (1 mg/kg, i.p for 21 days) to induce orofacial dyskinesia. Lycopene (5 and 10 mg/kg, p.o) was given daily 1 hour before haloperidol treatment for 21 days. Behavioral observations (vacuous chewing movements, tongue protrusions, facial jerking, rotarod activity, grip strength, narrow beam walking) were assessed on 0th, 7th, 14th, 21st day after haloperidol treatment. On 22nd day, animals were killed and striatum was excised for estimation of biochemical parameters (malondialdehyde, nitrite and endogenous enzyme (GSH), pro-inflammatory cytokines [Tumor necrosis factor, Interleukin 1β, Interleukin 6] and neurotransmitters level (dopamine, serotonin, nor epinephrine, 5-Hydroxyindole acetic acid (5-HIAA), Homovanillic acid, 3,4-dihydroxyphenylacetic acid. Haloperidol treatment for 21 days impaired muscle co-ordination, motor activity and grip strength with an increased in orofacial dyskinetic movements. Further free radical generation increases MDA and nitrite levels, decreasing GSH levels in striatum. Neuroinflammatory markers were significantly increased with decrease in neurotransmitters levels. Lycopene (5 and 10 mg/kg, p.o) treatment along with haloperidol significantly attenuated impairment in behavioral, biochemical, neurochemical and neuroinflammatory markers. Results of the present study attributed the therapeutic potential of lycopene in the treatment (prevented or delayed) of typical antipsychotic induced orofacial dyskinesia.

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1. Introduction

Tardive dyskinesia (TD) appeared as irreversible motor dysfunctional outcome of anti-psychotic treatment in schizophrenic patients (Grover et al., 2013). Tardive dyskinesia is an inevitable, iatrogenic, hyperkinetic movement disorder characterized by choriform, athetoid and rhythmic involuntary movements. Orofacial movements like vacuous chewing movements (VCMs), facial jerking, tongue protrusion, lip smacking are among principal features of Tardive dyskinesia (Ropke et al., 2014). Haloperidol and other antipsychotics are first choice of drug in the treatment of schizophrenia and long-term therapy of typical antipsychotics results in blockade of dopamine receptors and produce neurotoxicity due to generation of reactive oxygen species (ROS) and increased oxidative stress parameters and decreased neurochemical ranges (Balijepalli et al., 2001; Bishnoi et al., 2007). Haloperidol is widely recognized as valuable tool to study the neuropathology of Tardive dyskinesia. Chronic administration of haloperidol to rodents results in dopamine supersensitivity, oxidative stress, GABAergic hypo-function etc. Though the exact mechanism underlying Tardive dyskinesia neuropathology is not fully understood but the substantial role of oxidative stress and dopamine supersensitivity along with glutamate excitotoxicity, oxidative stress, GABAergic hypo-function are among well-established concepts (Thakur et al., 2014). Only approved drug for the management of Tardive dyskinesias yet available is Tetrabenazine but its use is associated with various adverse effects like depression, sedation etc. Therefore, there is an urgent need to find disease modifying drugs that may delay or apprehend the neurodegeneration in Tardive dyskinesia.

Lycopene, an aliphatic hydrocarbon, is one of the 600 known naturally occurring carotenoids and is found at high levels in

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tomatoes and tomato-based products (Visoli et al., 2003). Lycopene, a well-known potent antioxidant belongs to the family of carotenoids and is obtained from ripe tomatoes. It has been reported that lycopene has the potential of quenching singlet oxygen 100 times more efficiently than vitamin E and 125 times more than glutathione. Lycopene is well documented to exhibit potent neuroprotective, anti-proliferative, anti-inflammatory and cognition enhancing properties (Bishnoi et al., 2007; Kumar et al., 2009; Sachdeva and Chopra, 2015).

Therefore, the present study was designed to investigate the possible beneficial effects of lycopene on the behavioral, biochemical and neuroinflammatory changes induced by long-term treatment with haloperidol in rats.

2. Material and methods

2.1. Experimental animals

Male Wistar rats (250–280 g) obtained from central animal house of I.S.F. College of Pharmacy, Moga, Punjab (India) were used. The animals were kept in polyacrylic cages and maintained under standard laboratory conditions (room temperature 22 ± 1 °C and relative humidity of 60%) with 12 h light/dark cycle. The food and water were made available *ad libitum*. All the behavioral assessments were carried out between 9:00 and 17:00 h. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) and experiments were carried out in accordance with the guidelines of the Indian National Science Academy (INSA) for the use and care of 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, Ahmedabad, India) was dissolved in distilled water. Lycopene (Albro Pharmaceutical Pvt. Ltd, Muktsar, Punjab, India) was dissolved in 0.5% Sodium carboxymethylcellulose (CMC) which was always used freshly prepared. Lycopene (5 and 10 mg/kg) was given orally and haloperidol 1 mg/kg through i.p route. Doses were selected on the basis of previous studies in laboratory and those reported in the literature (Kumar et al., 2009; Sandhir et al., 2010; Qu et al., 2011). The study was performed in multiple phases as shown in experimental protocol. The animals were segregated into following group comprises of six animals in each group.

S. no.	Groups
1.	Control (DDW+CMC, per oral (p.o)
2.	Haloperidol (1 mg/kg, intraperitoneal (i.p)+CMC (0.5%, p.o)
3.	Haloperidol (1 mg/kg, i.p)+Lycopene (5 mg/kg, p.o)
4.	Haloperidol (1 mg/kg, i.p)+Lycopene (10 mg/kg, p.o)

All the behavioral parameters were observed on day 0, 7th, 14th and 22nd day of haloperidol treatment. Behavioral parameters were observed in sequence on each day starting with narrow beam walking at 9:00 a.m then rotarod activity, grip strength followed by VCMs, tongue protrusion and facial jerking in each animal.

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 the last behavioral assessment was done 24 h after the last dose of haloperidol i.e. on day 22.

2.4. Assessment of behavioral parameters

2.4.1. Assessment of orofacial movements

On the test day, the rats were placed individually in plexi glass (30 cm × 20 cm × 30 cm) cage for the assessment of oral dyskinesia. Animals were allowed for 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 frequencies. In the present study, VCM are referred to as single mouth opening in the vertical plane not directed towards physical material. 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 (Bishnoi et al., 2007; 2008; Grover et al., 2013; Thakur et al., 2014).

2.4.2. Rota-rod activity

The motor coordination and grip strength performance of the animals were evaluated using the rotarod apparatus. The rats were exposed to a prior training session to acclimatize them to rotarod performance. Rats were placed on a rotating rod having a diameter of 7 cm (speed 25 rpm). The cut off time was 180 s and the average time of the fall was recorded (Thakur et al., 2014).

2.4.3. Narrow beam walk test

With the beam-walking test, motor coordination and balance of rats were assessed by measuring the ability of animals to traverse a narrow beam to reach an enclosed safety platform. Narrow beam walk apparatus is used to detect gait abnormalities induced in dyskinesia and motor deficit in rats. The apparatus consists of 2-m wooden strips supported by two pedestals at each end. The pedestals are of different heights (42.5 and 100 cm) in order to allow for an inclination. This inclination is enough to stop animals from crawling over the beam. At the end of the inclined strip, a cage is placed so that the animals could step into the home cage and nesting material is kept in home cage to attract animals. It is important to make sure that the entire apparatus be placed at a height of at least 1 m above the ground, so as to make the beam along with their number of foot slips was recorded. If they did not complete the task or if they fall off the beam, or freeze, the rats were assigned a maximum latency of 60 s to cross the beam and maximum 6 foot slips (Colin and Hernandez, 1991)

2.4.4. Assessment of grip strength

Grip strength of the fore limbs was measured using digital grip force meter (DFIS series, Chatillon, Greensboro, NC, USA). The rat was positioned to grab the grid with the fore limbs and was gently pulled to record the grip strength (Thakur et al., 2014). The grip strength was recorded in Kgf.

2.5. Dissection and homogenization

On day 22, all the animals were killed by decapitation immediately 24 h after behavioral assessments. The brains were removed, and cerebellum was discarded. Brains were put on the ice

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