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Minocycline modulates neuroprotective effect of hesperidin against quinolinic acid induced Huntington's disease like symptoms in rats: Behavioral, biochemical, cellular and histological evidences

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ABSTRACT

Emerging evidences indicate hesperidin, a citrus flavanone, attenuates neurodegenerative processes and related complications. Besides its anti-oxidant properties, the other probable mechanisms which underpin its neuroprotective potential are still not clear. In light of emerging role of flavonoids in modulating oxidative stress and neuro-inflammation, the study has been designed to explore the possible neuroprotective effect of hesperidin and its combination with minocycline (microglial inhibitor), against quinolinic acid (QA) induced Huntington's disease (HD) like symptoms in rats. Unilateral intrastriatal administration of QA (300 nmol/4 μl) significantly reduced body weight, impaired behavior (locomotor activity, beam balance and memory performance), caused oxidative damage (increased lipid peroxidation, nitrite concentration, depleted super oxide dismutase and reduced glutathione), demonstrated mitochondrial dysfunction (decreased Complex-I, II, III, and IV activities), increased striatal lesion volume and altered the levels of TNF-α, caspase-3 as well as BDNF expression, as compared to sham group. Meanwhile, chronic hesperidin (100 mg/kg, p.o.) and minocycline (25 mg/kg, p.o.) treatment for 21 days significantly attenuated the behavioral, biochemical and cellular alterations as compared to QA treated (control) animals, whereas hesperidin (50 mg/kg, p.o.) treatment was found to be non-significant. However, treatment of hesperidin (50 mg/kg) in combination with minocycline (25 mg/kg) potentiated their neuroprotective effect, which was significant as compared to their effects *per se* in QA treated animals. Taken altogether, the results of the present study suggest a possible interplay of microglial modulation and anti-oxidant effect in neuroprotective potential of hesperidin against QA induced HD like symptoms in rats.

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1. Introduction

Huntington's disease (HD) is an autosomal neurodegenerative disorder caused by an expansion of the cytosine–adenine–guanine (CAG) repeat in the gene coding for the N-terminal region of the huntingtin protein (htt), leading to the formation of a polyglutamine stretch (mhtt) (Bano et al., 2011). The behavioral deficits manifest as typical involuntary choreiform movements, cognitive impairment and mood disorders, eventually compromising a person's daily functional abilities (Raymond et al., 2011). Unilateral quinolinic acid (QA) induced striatal lesions are highly reminiscent of histological (selective loss of GABAergic and cholinergic neurons) and neurochemical characteristics of HD in experimental animals. It is a well documented fact that over excitation of N-methyl-D-aspartate (NMDA) receptor following QA administration results in profound oxidative damage, lipid peroxidation, mitochondrial dysfunction and apoptosis (Estrada Sanchez et al., 2008; Perez-De La Cruz et al., 2012)

The role of microglial activation in the pathogenesis of HD has recently been addressed by clinical studies demonstrating a stark correlation between abnormal microglial activity and disease progression (Tai et al., 2007a). According to several study reports, microglial activation was found to be evident in pre-symptomatic HD gene carriers and can be detected up to 15 years before the onset of disease (Tai et al., 2007b). However the mechanism(s) by which mhtt causes the detrimental changes in microglial physiology are not clear yet. The localization of QA specifically to microglial cells following brain damage and subsequent increased expression of neuroinflammatory cytokines (interleukins, tumor necrosis factors) (Dihne et al., 2001; Ryu et al., 2005) has also been demonstrated in several *in vivo* studies (Lehrmann et al., 2001). However, neuroprotective potential of minocycline, a second generation semi-synthetic tetracycline derivative has recently been reported in various neurodegenerative conditions including

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HD (Lee et al., 2003; Wu et al., 2002; Chen et al., 2000). Besides, studies from our laboratory also demonstrated the neuroprotective potential of hesperidin in several neurodegenerative conditions including QA induced neurotoxicity in wistar rats (Kalonia et al., 2012; Kumar et al., 2012a). However, the mechanisms by which minocycline exerts neuroprotective effects in CNS disorders also incorporate the capacity to inhibit neuronal apoptosis (Lee et al., 2003; Wang et al., 2003) and free radical formation (Jiang et al., 2009).

Neuroprotective potential of hesperidin has been reported extensively in both *in vitro* as well as *in vivo* studies which is attributed primarily to its anti-oxidant and anti-inflammatory activities (Gaur and Kumar, 2010; Menze et al., 2012; Rainey-Smith et al., 2008). Besides, the possible involvement of nitric oxide mechanism in the neuroprotective potential of hesperidin has also been demonstrated by our own group (Gaur et al., 2011; Kumar and Kumar, 2010). Recently, microglial pathway in the neuroprotective effect of hesperidin has also been targeted (Koppula et al., 2012; Yamamoto and Saneyoshi, 2009), however, there is lack of convincing data around this hypothesis. Therefore, the present study has been designed to explore microglial pathway in the neuroprotective effect of hesperidin based upon its interaction with minocycline (microglial inhibitor) against QA-induced neurobehavioral, neurochemical, behavioral, and histopathological alterations in rats.

2. Materials and methods

2.1. Animals

Male wistar rats (250–300 g) bred in Central Animal House, Panjab University, Chandigarh were used in this study. The animals were kept under standard laboratory conditions, maintained on 12-h light/dark cycle and have free access to food and water. All the experimental procedures were performed between 9:00 and 17:00 hours. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of Panjab University (Protocol no. 282/30/8/12/UIPS-42) and carried out in accordance with the guidelines of Committee for the Purpose of Control and Supervision of Experimentation on Animals (CPCSEA), Government of India and Indian National Science Academy Guidelines for the use and care of experimental animals.

2.2. Intrastriatal administration of QA

The rats were anesthetized with thiopental sodium (45 mg/kg, i.p.) and placed in a stereotaxic apparatus. The surface of the skull was exposed by making incision on the scalp. A 1–2 mm diameter hole was made in the skull for microinjection using a small hand drill at anterior +1.7 mm; lateral ±2.7 mm; ventral −4.8 mm from bregma and dura as described by Paxinos and Watson (2007). QA (300 nmol/4 μl) (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in normal saline (pH 7.4) and administered unilaterally in right striatum *via* a 28-gauge stainless steel needle attached to a 10 μl Hamilton syringe. A total volume of 4 μl of QA was delivered slowly over a period of 2 min and injection needle was left in place for another 2 min to prevent back diffusion of the injected drug solution.

2.3. Drug and treatment schedule

Hesperidin (25, 50, and 100 mg/kg) (Sigma-Aldrich, St. Louis, MO, USA) and minocycline (25 mg/kg) (Wyeth Ltd., Mumbai, India) were suspended in 0.25% (w/v) sodium carboxy methyl cellulose (CMC) solution and administered *per oral* in a constant volume of 0.5 ml per 100 g of body weight. Each group received treatment daily in the morning 10:00 hours, for 21 days starting from day 1 after recovery from experimental procedure (Fig. 1). Doses of hesperidin and minocycline were selected on the basis of our previous study reports (Gaur et al., 2011; Kalonia et al., 2012; Kumar and Kumar, 2010). The entire protocol involves seven treatment groups with eleven animals ($n=11$) in each treatment arm (Table 1). Several studies in our laboratory reported that, hesperidin (100 mg/kg, p.o.) and minocycline (100 mg/kg, p.o.) *per se* groups did not exhibit any significant difference in the behavioral, biochemical and mitochondrial parameters as compared to the naive/sham animals (Kalonia et al., 2012; Kumar and Kumar, 2010). Therefore, *per se* groups for hesperidin and minocycline at the above mentioned doses have been excluded from the present study protocol in order to minimize the use of experimental animals as per CPCSEA guidelines and protocol has been designed with an assumption that hesperidin and minocycline do not possess any *per se* effect in rats.

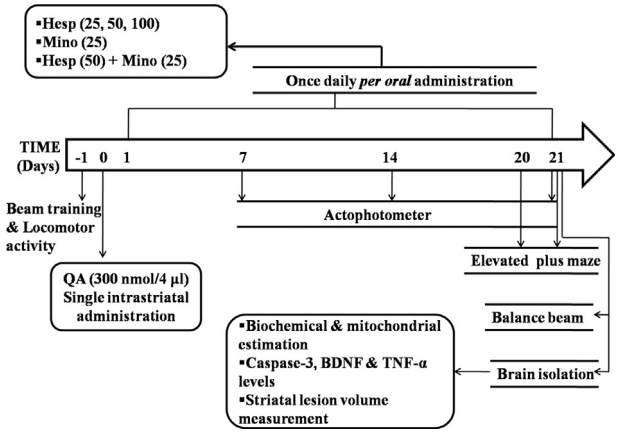

Fig. 1. Experimental design.

2.4. Measurement of body weight

The body weights of the animals were recorded after intrastriatal administration of QA (day 1) and on the last day of the study (21st day). Percentage change in body weight was calculated as

$$\text{Percentage change in body weight} = \text{body weight}\frac{(\text{day21}-\text{day1})}{(\text{day1})} \times 100$$

2.5. Behavioral assessments

2.5.1. Assessment of gross behavioral activity (locomotor activity)

The locomotor activity was assessed using actophotometer (IMCORP, Ambala, India) on weekly intervals. Animals were placed individually in the activity chamber for 3 min as a habituation period before recording actual motor activity for next 5 min. The instrument consisted of a closed arena equipped with 12 infrared light-sensitive photocells in two rows (six in each row), at a distance of 3 cm and 9 cm respectively and values expressed as counts per 5 min. The beams in actophotometer cut by the animals were taken as the measure of movements. The values were expressed as counts per 5 min (Kumar et al., 2012b).

2.5.2. Balance beam walking (hind limb functioning) test

This behavioral test assesses the motor performance of animals by their ability to walk across an elevated tapered beam of increasing the difficulty provided with an under-hanging ledge which serves as a crutch for the animal to use when there is a deficit. The setup

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