Available online on 15.08.2021 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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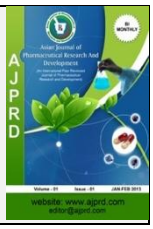

Open Access Research Article

Evaluation of anticataleptic activity of Hydroxytyrosol on Haloperidol induced Catalepsy in Experimental Animal

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A B S T R A C T

Catalepsy is a symptom resulting from problems with the nervous system, and causes muscular rigidity. People with the symptoms may also be less sensitive to touch and have a decreased sensitivity to pain. Catalepsy generally causes people to be unresponsive to speech. It is similar to catatonia, a condition marked by strange movements, lack of movement, and/or general non responsiveness. However, it typically has an underlying physiological cause and does not cause stereotyped movements.

Keywords-Catalepsy, Haloperidol, Scopolamine, Hydroxytyrosol.

A R T I C L E I N F O: Received 25 June 2021; Review Complete; 30 July 2021 Accepted; 08 August 2021 Available online 15 August 2021

Cite this article as:

Mira T. Bansode, V. J. Chaware, V. K. Redasani, Evaluation of anticataleptic activity of Hydroxytyrosol on Haloperidol induced Catalepsy in Experimental Animal., Asian Journal of Pharmaceutical Research and Development. 2021; 9(4):63-74.
DOI: http://dx.doi.org/10.22270/ajprd.v9i4990

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INTRODUCTION-

Catalepsy is a condition characterized by inactivity, decreased responsiveness to stimuli and a tendency to maintain an immobile posture. It may be associated with the nervous system drug toxicity, psychotic disorders and other conditions. (1) Catalepsy is the neurodegenerative disease of unknown etiology and characterized by motor symptoms of tremor, rigidity, bradykinesia, and postural instability. Catalepsy is characterized by an abnormal basal ganglia activity. Non-motor comorbidities, such as cognitive impairments (the comorbidity of anxiety and depression like Parkinson's disease) are likely the result of an intricate interplay of multi-system degenerations and neurotransmitter deficiencies extending beyond the loss of dopaminergic nigral neurons. (1)(3)

It is an iatrogenic disorder that occurs following chronic anti-psychotic drug treatment that is characterized by motor symptoms dysfunction that is extrapyramidal side effects. When the effect extends beyond the oro-facial region there may be involuntary laryngeal changes and consequent vocalization. Breathing can be affected, as well as the flexion and extension of shoulders, fingers, wrists, hips, knees, ankles and toes. These effects are challenging in social settings, but can also interrupt daily life and personal care. These symptoms are rarely present during sleep and can be halted during attention tasks, however most commonly individuals affected by tardive dyskinesia are not aware of the presence of their symptoms or their ability to voluntarily modulate symptoms. (1)(2)

SYMPTOMS OF CATALEPSY

- Extremely rigid body posture
- Decreased sensitivity to pain
- Limbs that stay in the same position when they are moved
- Slower bodily functions
- Particularly breathing
- Decreased muscle control, or complete loss of muscle control (Costall & Naylor, 1974).

Causes

- Biochemical factor: Low level of neurotransmitter Serotonin, dopamine, norepinephrine.
- Genetic factor: Family member with schizophrenia disorder or psychotic disorder.
- Serious illness: neurological disorders such as Parkinson's disease and epilepsy.
- Substance risk for catalepsy: Medication, substance abuse, drug withdrawal.

MATERIALS AND METHOD-

Animals and housing condition*:*

The experiments will be conducted with Wistar male rats of 110–250 g and 2–3 months old. Female rats are excluded from the present study since estrogen has been reported to possess neuroprotective property and this might mask development of Catalepsy. These animals will be procured from registered breeder and will be acquainted in the quarantine area for one week. After acquaintance, animals will be transferred to the standard laboratory conditions of22±2°Ctemperature,50±15%relativehumidity,12hr.dark/12hr.light)cycleandtheanimals will have free access to pellet diet & water will be provided *ad libitum*. The study protocol will be presented to the IAEC for approval (Dhingra, 2017).

Drug and Reagent- Hydroxytyrosol was acquired from Rajesh Chemicals CO. Mumbai. Scopolamine was obtained from Recipharm Pharmaservices Pvt. Ltd. Bengalore. Haloperidol (serenac 0.25) tablets were procured from RPG Life science Ltd. Gujarat. All other chemicals used were of analytical grade.

Study Design-

The 36 male Albino Wistar rats were divided into six groups: group 1 (control group), group 2 (Catalepsy inducedgroup), group 3 (standard group), groups 4, 5 and 6 (treatment groups). Following Haloperidol administration, standard group was administered with Scopolamine at a dose of 1 mg/kg in oral and treatment groups 4, 5 and 6 were administered Hydroxytyrosol with the dose of 25 mg/kg (Low dose) and 50 mg/kg(Intermediate dose) and 100 mg/kg (High dose) respectively oral for 21 days.

EXPERIMENTAL PROCEDURES

Haloperidol induced catalepsy

A cataleptic behavior will be measured with a high bar test method. Catalepsy score will be measured each hour for 4 h after haloperidol administration, by gently placing both the forepaws of the rat over a metal bar (diameter 2–5 mm) situated 6 cm above the tabletop. The intensity of catalepsy will be assessed by counting the time in seconds until the rat brought both forepaws down to the tabletop, with a maximum cutoff time of 180 s. Finally, scores at different time points (0, 60, 120, 180 and 240 min after haloperidol injection) will be added and expressed as a cumulative catalepsy score for comparison purpose. In all the experiments, the scorer will be blind to the treatment given to the rat. (Naidu & Kulkarni, 2002) (Sanberg et al., 1988).

SCORING OF CATALEPSY –

Cataleptic animal maintaining this position for a period of time dependent upon the degree of catalepsy. If the animal maintained the imposed posture for at least 20s it was said to be cataleptic and given one point.

Scoring will be modified from that used by Costall and Naylor (1974). Animals maintaining the cataleptic posture from 0 s to 10 s scored 0; 10 s to 30 s = 1; 30 s to l min=2; l min to 2 min=3; 2 min to 3 min=4; 3 min to ∞ =5. Animals will be tested for catalepsy 0.5, 1.0, 2.0,

3.0 and 4.0h after haloperidol treatment (Costall & Naylor, 1974)

Statistical Analysis

The statistical analysed by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison test and Dunnett's multiple comparison test. The statistical analyzed by two-way analysis variance followed by Bonferroni Posttests. Data expressed as group mean with standard error mean (mean ± SEM). Data was also compared within group; statistical analysis was done by using paired t-test. P<0.05 was considered to be significant. Statistical analysis and graphical presentation of data was done with Graphed prism-5 software.

RESULTS

Effect of Hydroxytyrosol on catalepsy Score by using High Bar Test

Day 7 : Effect of Hydroxytyrosol on catalepsy activity

Table 1: Effect of Hydroxytyrosol on Catalapsy Score. (7 Day)

Groups	Time (Day 7)				
	30 min	60 min	120 min	180 min	240 min
Normal Control	0.0000±0.0	0.1665 ±0.0	0.0000	0.1666 ±0.0	0.1667 ±0.0
Negative Control	3.168±0.6945***	3.001 ±0.6571***	3.332 ±0.7301***	3.166 ±0.6936	2.668 ±0.5841***
Positive Control	1.500±0.3286**##	1.50 ±0.327**##	1.66 ±0.3651**##	1.833 ±0.4014***#	1.500 ±0.3284***
Low Dose 25mg	2.499±0.5476***	2.668 ±0.5839***	2.834 ±0.6206***	2.332 ±0.5109***	2.334 ±0.5109***
Intermediate Dose 50mg	1.833±0.4014***#	2.333 ±0.5109***	2.333 ±0.5109***#	2.166 ±0.4746***	2.001 ±0.4381
High Dose 100mg	1.832±0.4016***#	2.001 ±0.4381***	2.0001±0.4381***	2.001 ±0.4381***	1.666 ±0.3649

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicatecomoarision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Day 14

Effect of Hydroxytyrosol on catalepsy activity –

Table 2: Effect of Hydroxytyrosol on Catalapsy Score. (14 Day)

Groups	Time (Day 14)				
	30 min	**60 min**	**120 min**	**180 min**	**240 min**
Normal Control	0.0 ± 0.0	0.0 ±0.0	0.0 ± 0.0	0.0 ±0.0	0.0 ±0.0
Negative Control	2.666 ± 0.6406***	4.0 ± 0.9607***	3.5001 ± 0.8407***	3.332 ± 0.8007***	3.166 ± 0.7607***
Positive Control	1.501 ± 0.3602**#	2.166 ± 0.5205***###	1.832 ± 0.4405***###	1.666 ± 0.4004***###	1.500 ± 0.3604***###
Low Dose 25mg	2.332± 0.5605***	3.001 ± 0.7205***	2.666 ± 0.6406***@	2.501 ± 0.6006***	2.668 ± 0.6404***
Intermediate Dose 50mg	2.000 ± 0.4805***	2.500 ± 0.6005***##	2.333 ± 0.5605***#	2.167 ± 0.5205***#	2.167 ± 0.5205***
High Dose 100mg	1.667 ± 0.4004***###	2.333 ± 0.5605***###	2.000 ± 0.4805***###	1.833 ± 0.4405**##	1.500 ± 0.3604**###

Day 21

Effect of Hydroxytyrosol on catalepsy activity-

Table 3: Effect of Hydroxytyrosol on Catalapsy Score. (21 Day)

Groups	Time (Day 21)				
	30 min	**60 min**	**120 min**	**180 min**	**240 min**
Normal Control	0.0 ± 0.0	0.0 ±0.0	0.0 ± 0.0	0.0 ±0.0	0.0 ±0.0
Negative Control	1.666 ± 0.4902***	2.666± 0.7355***	3.332 ± 0.9805***	2.666 ± 0.7355***	2.166 ± 0.5882***
Positive Control	0.832 ± 0.2452	1.000± 0.2452###	1.500 ± 0.4412***##	1.167 ± 0.2493*###	1.333 ± 0.3433**
Low Dose 25mg	1.500 ± 0.4412***	2.000 ± 0.5392***@	2.500 ± 0.7355***@	2.332 ± 0.6375***@@	1.882 ± 0.4904***
Intermediate Dose 50mg	1.332 ± 0.3923***	1.833 ± 0.4902**	2.166 ± 0.6375***#	2.166 ± 0.5882***@	1.500 ± 0.3923***
High Dose 100mg	1.333 ± 0.3925***	2.167 ± 0.5883***@@	1.667 ± 0.4903***###	1.667 ± 0.4413***#	1.500 ± 0.3922**

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicatecomparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Effect of Hydroxytyrosol on locomotor activity by using actophotometer

Day 7

Effect of Hydroxytyrosol on locomotor activity

Table 4: Effect of Hydroxytyrosol on Locomotor Activity. (7 Day)

Groups	Locomotor activity counts/10min (Day 7)
Normal Control	482.0 ± 3.917
Negative Control	267.0 ± 1.879***
Positive Control	422.5 ± 1.785***##
HT Low Dose (25mg)	311.5 ± 1.117***##@@
HT Intermediate Dose (50mg)	334.8 ± 2.404***##@@
HT High Dose (100mg)	388.8 ± 2.142***###@@

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicate comparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Day 14

Effect of Hydroxytyrosol on locomotor activity

Table 5: Effect of Hydroxytyrosol on Locomotor Activity. (14 Day)

Groups	Locomotor activity counts/10min (Day 7)
Normal Control	408.7 ± 3.135
Negative Control	192.5 ± 1.196***
Positive Control	433.8 ± 1.726***##
Low Dose 25mg	324.8 ± 1.667***##@@
Intermediate Dose 50mg	346.7± 2.141***##@@
High Dose 100mg	390.8 ± 1.712***###@@

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicate comparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Day 21

Effect of Hydroxytyrosol on locomotor activity

Table 6: Effect of Hydroxytyrosol on Locomotor Activity. (21 Day)

Groups	Locomotor activity counts/10min (Day 7)
Normal Control	468.8 ± 1.077
Negative Control	143.7 ± 2.485***
Positive Control	442.5 ± 3.843***##
Low Dose 25mg	335.6 ± 2.357***##@@@
Intermediate Dose 50mg	360.7 ± 2.954***###@@@
High Dose 100mg	425.3 ± 4.728***###@@

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicate comparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Biochemical Parameter-

Effect of Hydroxytyrosol in Dopamine level (µg/mg)

Effect of Hydroxytyrosol on Dopamine level from rat brain tissue

Table 7: Effect of Hydroxytyrosol on Dopamine Level (µg/mg).

Groups	Dopamine level µg/mg of brain tissue
Normal Control	4.261± 0.24001
Negative Control	1.784 ±0.06501***###
Positive Control	6.574 ± 0.32501***###
Low Dose 25mg	3.501 ± 0.05001*###@@
Intermediate Dose 50mg	4.469 ± 0.3201###@@
High Dose 100mg	6.239 ± 0.6501***###@@

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicate comparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Effect of Hydroxytyrosol in Serotonin level (µg/mg)

Effect of Hydrotyrosol on Serotonin level from rat brain tissue

Table 8: Effect of Hydroxytyrosol on Serotonin Level (µg/mg).

Groups	Serotonin Level µg/mg of brain tissue
Normal Control	16.9079 ± 0.12500
Negative Control	6.794 ± 0.21500***
Positive Control	19.371 ± 0.31000*###
Low Dose 25mg	12.669 ± 0.34500***###@@@
Intermediate Dose 50mg	14.679 ± 0.31000***##@@@
High Dose 100mg	16.989 ± 0.21500***###@@

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicate comparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

Effect of Hydroxytyrosol in SOD level (µg/mg)

Effect of Hydroxytyrosol on SOD level from rat brain tissue

Table 9: Effect of Hydroxytyrosol on SODLevel (µg/mg).

Groups	SOD Level µg/mg of brain tissue
Normal Control	61.231 ± 0.20501
Negative Control	23.179 ± 0.97501***
Positive Control	54.479 ± 0.37001###
Low Dose 25mg	34.979 ± 0.19001***###@@@
Intermediate Dose 50mg	42.659 ± 0.44501***###@@@
High Dose 100mg	52.179 ± 0.29501**###@@

All values are presented as mean ± SEM. Analysis was performed using one way ANOVA followed by Bonferroni multiple comparision posttest. *indicate comparision with control group. #indicate comparision of negative control group. @indicate comparision with positive control. */#/@indicate p<0.05, **/##/@@ indicate p<0.01 and ***/###/@@@indicate p<0.001.

CONCLUSION

In normalizing the various parameters in Catalepsy induced rats, the impact of Hydroxytyrosol therapy with medium (50mg/kg) and high(100mg/kg)was observed to be similar with standard treatment.

In haloperidol induced Catalepsy animals, Hydroxytyrosol recovered the dopamine Serotonin Superoxide dismutase level. Thus, Hydroxytyrosol might be beneficial in managing Catalepsyconditionduetonumerouspharmacologicalactivities includingantioxidant,anticancer,woundhealing,andprotective action against hyperglycemia and hyperlipidemia. By their rich antioxidant activity, Hydroxytyrosol likely promoted protective action against the Catalepsy condition.

Discussion-

Neuroleptics produce two main type of motor disturbances in humans-catalepsy and tardive dyskinesia, collectively called as extrapyramidal side effects, which result directly or indirectly from the blockade of dopamine D2 receptors. These effects constitute the main disadvantages or the therapeutic use of typical neuroleptics. Catalepsy is a characteristic consequence of anti-psychotic drug administration to rats. Most commonly the drug-induced cataleptic effect in rats has been characterized as a reflection of the potential of these drugs to produce extra-pyramidal side effects in humans including Parkinsonianism, akanthesia and dyskinesia.

Haloperidol treatment for 21 successive days significantly induced catalepsy in rats, as indicated by significant increase immobility. This is also supported by the earlier study where haloperidol (1mg/kg) administered once daily in the morning for a period of 21 successive days produced decrease in movements in rats. It has been reported in the literature that chronic use of neuroleptics may lead to imbalance in the production and detoxification of free radicals. Catalepsy is also characterized by accumulation of oxidative damage mainly in the brain due to its high energy metabolism and the relative low activity of antioxidative defence mechanism.

Many factors are proposed for causing catalepsy, such as abnormalities in function of neurotransmitters receptors (e.g., Adenylyl cyclase-cAMP pathway), dysregulation of hypothalamic pituitary adrenal axis (cortisol), changes in the brain monoaminergic transmission (e.g.,5-HydroxyTryptamine, Dopamine, Norepinephrine), increased proinflammatory cytokines (e.g., interleukin-6, tumor necrosis factor-α), increased oxidative stress (e.g., lipid and DNA damage), increased nitric oxide (NO).

In this study, we used two animal models. Actophotometer and high bar test. All the models are widely accepted behavior models for assessing pharmacological anticataleptic activity. All animal were treated with Hydroxytyrosol along with inducer Haloperidol for every model and activity was check on every (i.e., 7^{th},14^{th},21^{th}).

Hydroxytyrosol showed significant anticataleptic activity at doses of 25mg/kg,50mg/kg, and 100mg/kg.

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