Effect of chronic administration of low dose aspirin on haloperidol induced catalepsy in rats

Sir,

Neuroleptics are routinely used in the management of schizophrenia and other affective disorders. Unfortunately, their use is often associated with distressing extra-pyramidal side effects (EPS) such as Parkinsonism and tardive dyskinesia. One of the best preclinical model for evaluation of neuroleptic induced EPS is haloperidol-induced catalepsy in rats. The cataleptic immobility induced by typical neuroleptics (e.g., haloperidol) in animals is a good behavioral model to study the nigrostriatal function and its modulation by different neurotransmitters. Haloperidol-induced catalepsy occurs due to the blockade of dopamine receptors in the nigrostriatal pathway and reduced dopaminergic neurotransmission.[1]

Haloperidol induced catalepsy test is widely used to study the neuro-pharmacology of extrapyramidal function. Dysregulation of dopaminergic neurotransmission is one of the patho-physiological mechanisms responsible for EPS. Bala *et al.,* reported that prostaglandins modulate the dopamine release in the striatum, the principle area involved in the pathophysiology of EPS. They reported that rats pretreated with prostaglandin synthesis stimulators, phenoxymethyl penicillin (2, 4, and 8 mg/kg, i.p.) and levamisole (2.5, 5, and 10 mg/kg, i.p.) showed a dose related potentiation of haloperidol induced catalepsy.[2] An inhibitory effect of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) on haloperidol induced catalepsy seems plausible. Earlier reports suggest that administration of aspirin in analgesic dose range decreased haloperidol induced catalepsy in mice in a dose dependent manner.[3] So, the present study was carried out to evaluate the effect of chronic administration of low dose aspirin on haloperidol induced catalepsy.

Table 1: Catalepsy scores

Total time of catalepsy (sec)	Score	Total time of catalepsy (sec)	Score
0-10	0	121-150	3
11-30	0.5	151-180	3.5
31-40	1	181-210	4
61-90	1.5	211-240	4.5
91-120	2	240-	5

Experimentally naive, male, Sprague Dawley albino rats weighing between 150 and 200 g were used. The rats were maintained under standard conditions of temperature (25°C±5°C), relative humidity (55±10%) and a 12/12 h light/dark cycle. The rats were fed with commercial rat pellet diet manufactured by Pranav Agro Food, Pune and water *ad libitum*. The rats were procured from institutional animal house and the study was approved by the Institutional Animal Ethics Committee.

The rats were grouped as follows: Group I (n=6) served as control. Group II (n=6): Each rat was given aspirin (6.75 mg/kg p.o.) (dose is equivalent to 75 mg dose in human beings) as single daily dose for 8 days. Group III (n=6): Each rat was given aspirin (10 mg/kg p.o.) as single daily dose for 8 days. Group IV (n=6): each rat was given aspirin (13.5 mg/kg p.o.) (dose is equivalent to 150 mg dose in human beings) as single daily dose for 8 days. On ninth day, haloperidol (1.5 mg/kg i.p.) was administered to the rats and catalepsy score was measured every hour for 6 hours using the 'standard bar test'. The scoring was done [Table 1].[4]

The data were analyzed using Kruskal-Wallis test followed by Dunn's test. P<0.05 was considered significant. Maximum catalepsy score at any point of time in each rat was taken for comparison. Catalepsy score was 5±0 (mean ±S.D.) in group I. It decreased to 2.41±0.7, 1.3 ±0.4, 0.75±0.2 in group II, III, and IV, respectively. Chronic administration of low dose aspirin significantly decreased catalepsy score (P<0.001) in a dose dependent manner.

Interest in studying catalepsy in animals is because of its similarity to the symptoms of human disorders like Parkinsonism, catatonic schizophrenia, and brain damage involving parts of striatum. It is also a common behavioral tool to study the central neurotransmitters. It is evident from the biochemical, electrophysiological, and behavioral studies that prostaglandins influence functioning of the nigrostriatal and mesolimbic dopaminergic systems. Prostaglandin E1 (PGE_1) has been reported earlier to induce catalepsy in several animal species, including rats, both on peripheral and central administration. Prostaglandin synthesis inhibitors are known to inhibit cataleptic effects of morphine and cannabis.[5]

Our study suggests that chronic administration of low dose aspirin significantly decreases haloperidol induced catalepsy in rats in a dose dependant manner. Since low dose aspirin decreases the thromboxane A_2 levels by inhibiting cyclooxygenase enzyme, it is likely that the decrease in catalepsy score could be associated with decreased thromboxane A_2 level. It is reported that administration of aspirin in analgesic dose range decreased haloperidol induced catalepsy in mice in a dose dependent manner.[3] Literature also suggests that striatal 3,4-dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindole 3 acetic acid (5-HIAA) levels are increased by haloperidol, but dopamine and 5-HT levels remain unchanged. Aspirin decreases elevated DOPAC level in the striatum. Modulation of DOPAC level by aspirin is responsible for the dose dependent decrease in haloperidol induced catalepsy in mice.[6] It is worth mentioning that no information exists on the possible functional interplay between thromboxane A_2 and the central dopaminergic system. Since both these transmitters have been implicated in haloperidol induced catalepsy in rats, such studies are warranted for better understanding of the complexities of synaptic transmission in the central nervous system.

Arijit Ghosh, V.R. Dhumal[1], Abhijeet V. Tilak[2], Amarinder Singh[2], Meghna Pandey[2], Abhijit A. Bondekar[2]

Department of Pharmacology, N.R.S. Medical College, Kolkata, [1]Modern Dental College, Indore, [2]Padmashree Dr. D.Y. Patil Medical College, Pimpri, Pune, India

Address for correspondence:
Arijit Ghosh, Flat no-B-7/1, Iswarchandra Niwas, 68/1 Bagmari Road, Kolkata – 700 054, India. E-mail: drarijitghosh@gmail.com

REFERENCES

1. Pemminati S, Nair V, Dorababu P, Gopalakrishna HN, Pai M. Effect of ethanolic leaf extract of *Ocimum sanctum* on haloperidol-induced catalepsy in albino mice. Indian J Pharmacol 2007;39:87-9.
2. Bala Lall S, Tekur U, Sen P. Effect of drugs influencing synthesis of prostaglandins on haloperidol-induced catalepsy in rats. Indian J Physiol Pharmacol 1984;28:219-22.
3. Ono N, Saito R, Abiru T, Matsushita Y, Kamiya H. Effect of aspirin on haloperidol-induced cataleptic behavior in mice. Neuropharmacology 1988;27:327-9.
4. Rao NV, Pujar B, Nimbal SK, Shantakumar SM, Satyanarayana S. Nootropic activity of tuber extract of Pueraria tuberosa (roxb). Indian J Exp Biol 2008;46:591-8.
5. Bhattacharya SK, Rao M, Bhattacharya D. Prostaglandin E_1 induced catalepsy in the rat: Role of putative neurotransmitters. Pharm Res 1984;1(5):229-31.
6. Ono N, Abiru T, Sugiyama K, Kamiya H. Influences of cyclooxygenase inhibitors on the cataleptic behavior induced by haloperidol in mice. Prostaglandins Leukot Essent Fatty Acids 1992;46:59-63.

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/0976-500X.83292