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Original Article

STUDY TO EVALUATE THE ROLE OF SEROTONIN IN PARKINSONIAN SYMPTOMS

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ABSTRACT

Objective: Study to evaluate the role of serotonin in Parkinsonism by using olanzapine (an atypical antipsychotic drug) on haloperidol-induced extrapyramidal symptoms (EPS) in Swiss albino mice.

Methods: EPS like catatonia and rigidity were produced in Swiss albino mice by intraperitoneal (i. p) injection of haloperidol. Olanzapine was given as a pretreatment for acute and sub-acute basis (15 d orally) and effects were compared in terms of protection against catatonia like abnormal movements. They were analyzed statistically by ANOVA followed by post hoc Tukey's test using SPSS 20 software.

Results: There was no improvement in catatonia scores on the acute study, but on subacute (15 d) intervention a moderate improvement in the combination group (15-20 %) was seen as compared to haloperidol alone.

Conclusion: Low-dose olanzapine due to serotonin antagonism and probable partial D_1 agonist actions may have the potential to improve the features of Parkinsonism. Further, it can have advantages over selective serotonin reuptake inhibitors (SSRI) for antidepressant activity in above disease.

Keywords: Haloperidol, Dopamine receptor subtypes (D_1 and D_2), Serotonin receptor subtypes ($5HT_{1-7}$), EPS, Parkinsonism Disease (PD)

INTRODUCTION

Parkinsonism has been considered a slowly developmental neurodegenerative disorder with loss of the dopaminergic neurons of nigrostriatal tracts [1, 2]. The predominant primary features of Parkinsonism Disease (PD) include abnormal movements like akinesia, tremors and rigidity. Other than primary features, patients also frequently suffer from psychosis, Levodopa-Induced Dyskinesia (LID), dementia and depression too. The symptoms of psychosis and LID may be due to [3] high dopamine levels during initial periods of therapy while depression may be secondary to serotonin deficiency.

The normal physiology of basal ganglion is complex [3]. There are serotonin projections from the dorsal horn raphe (D. H. R) to the basal ganglion, motor cortex and various other parts of the midbrain. Basal ganglion has an input unit at the level of the striatum. Through direct pathways involving D_1 stimulatory receptors, it sends facilitator signals to substantia nigra pars reticular is (SNPR) and globes pallidum medialis (GPM) for thalamocortical motor activity, while through D_2 receptors involving indirect pathways via globus pallidus lateralis and sub thalamic nucleus (GPL and STN) sends inhibitory signals to SNPR and GPM.

These both nuclei act as output pathway for basal ganglion. Stratum also receives dopamine input from substantia nigra pars compacta (SPNC). Striatum has a further nice balance of dopamine and acetylcholine activity too. There is the role of other neurotransmitters like dopamine, glutamate, and Gamma Amino Butyric Acid (GABA) etc. Out of these primary features, akinesia or bradykinesia are due to the lack of initiative efforts brought by dopamine. Due to a relative excess of acetylcholine as compared to dopamine at striatum, rigidity and tremors are seen which are best treated by centrally acting anticholinergic drugs like tri hexyphenidyl and benztropine.

The main idea which motivated us for the above work was marked low levels of serotonin in basal ganglion in PD patients. Further, a probable inhibitory effect of serotonin over dopamine functions has also been mentioned. So still an unresolved issue till date, we planned a study to evaluate the role of sub-therapeutic dose of olanzapine (with serotonin antagonism) on haloperidol-induced EPS.

MATERIALS AND METHODS

Drugs

Inj Serenace (Haloperidol 5 mg/ml-RPG LIFE), Tab Ozepam (Olanzapine 0.5 mg-INNOVA Pharmaceuticals), Distilled water (Core Pharmaceuticals), syringes and needles. Drugs were purchased through their local distributors.

Animals

Adult Swiss albino mice (20-30g) of either sex were procured from the central animal house, M. G. M. Medical College, Indore (M. P) and acclimatized for a period of 7 d at room temperature (25±2 °C) and 50±15% relative humidity. They were housed in a standard cage and maintained on standard pellets and water ab libitum. The animals were used as per standard animal care guidelines. The study was carried out in the department of pharmacology, M. G. M. Medical College Indore (M. P). The study protocol was approved by the institutional animal ethics committee (IAEC) registered with CPCSEA (Reg. No. 709).

Methods

It was an experimental study on Swiss albino mice, which were induced catatonia by using haloperidol [4]. All the drugs were given by intraperitoneal route (i. p) injection except subacute intervention where olanzapine was given orally. (i) Total no of mice 24 were randomly divided into 4 groups (n=6). They were given drugs by I. P route and treated as follows-Group I-Control-Haloperidol (1 mg/kg). Group II-standard group-Trihexyphenidyl 10 mg/kg and Haloperidol 1 mg/kg. Group III-Olanzapine 0.5 mg/kg alone and Group IV-Olanzapine and Haloperidol in above doses. After half an h of olanzapine (test drug), Haloperidol was given, and catatonia responses were assessed at 1/2, 1 and 2 h respectively. (ii) In subacute part of study olanzapine was given by oral route (0.5 mg/kg) for 15 d and catatonia was reassessed in the above groups. In both studies, scoring was done in animals where catalepsy was maintained for more than 60 seconds and maximum time of catatonia out of 3 responses in each animal was compared. A cutoff time of 1100 s was kept in all the groups. Statistical analysis was done by ANOVA followed by posthoc Tukey's test.

Table 1: Effects of acute olanzapine on haloperidol-induced catatonia

Group (n=6)	Dose (mg/kg)	Mean catatonia scores		
		30 min	60 min	120 min
Group I-Haloperidol	1	10.5±2.2	11.22.3	11.51.5
Group-II Haloperidol+trihexiphenidyl	1+10	3.2±0.25 [a]	3.5±1.2[a]	3.5±0.56[a]
Group III-0lanzapine	0.5	0±00[a]	0±00[a]	0±00[a]
Group IV-Haloperidol+olanzapine	1+0. 5	10.5±1.2	11.56±1.33	10.35±.23

ANOVA with multiple tukey's test, [a]p<0.05as compared to controls, Results show that there was no change in catatonia scores due to olanzapine at all intervals of time.

Table 2: Effects of olanzapine (subacute) on haloperidol induced catatonia

Group (n=6)	Dose (mg/kg)	Mean catatonia scores		
		30 min	60 min	120 min
Group I-Haloperidol	1	10.5±1.1	11.3±1.3	9.35±1.5
Group-II Haloperidol+trihexiphenidyl	1+10	3.5±0.57[a]	3.3±0.25[a]	2.5±0.55[a]
Group III–Olanzapine	0.5	0[a]	0[a]	0[a]
Group IV-Haloperidol+olanzapine	1+0.5	7.5±0.79[a,b]	8.81±0.2[a,b]	7.2±1.2[a,b]

ANOVA with multiple Tukey's test, [a] p<0.05as compared to Group I, [b]p<0.05as compared to Group I.

RESULTS

Statistically, there was no significant change in catatonia scores on acute doses (table-1) while 15-20% reduction in catatonia scores (p<0.05) as compared to haloperidol alone (table-2). While onsub acute intervention, olanzapine significantly reduced the catatonia scores. Thus, as per our study it is expected to improve the primary symptoms of PD. The overall impact of our study shows a significant improvement and reduction in catatonia scores.

DISCUSSION

The findings, which motivated us to exactly ascertain the probable role of serotonin in Parkinsonism were-(i) there was marked decrease in the level of serotonin in various parts of brain including basal ganglion in PD patients [5]. (ii) Use of ondansetron (a $5HT_3$ antagonist drug) as standard drug in models of drug induced EPS. [6].(iii) Sarizotan which is a $5HT_{1A}$ agonist and recently indicated for the control of symptoms of PD patients [7].

Review of literature regarding the correlation between serotonin and dopamine

Literature has mentioned about a probable inverse relation and predominant inhibitory role of serotonin over dopamine function as can be elicited by following examples-(1) In patients of depression where low levels of serotonin are responsible for sadness of mood, these consequently are associated with high levels of dopamine in the mesolimbic system and ventral prefrontal cortex (PVC) which may be responsible for the aggression and irritable impulsive behavior [8-10]. (2) Another supporting evidence arises from use of atypical antipsychotic drugs [11] like clozapine, olanzapine and risperidone, which at antipsychotic doses have more of $5HT_{2A/C}$ blocking property as compared to dopamine (serotonin antagonism with consequent high dopamine levels at PFC, thus they are more useful in negative and cognitive symptoms) and also associated with less of EPS. We expect these drugs with serotonin antagonistic property to improve the levels of dopamine at basal ganglion too. $5HT_{2A/C}$ sub receptors are widely distributed and are also found at the level of direct pathways (fibers to thalamic unit) of basal ganglion, there are documented evidences of them having an inhibitory role over the dopamine functions through GABA [12].

(3) The treatment of depression with drugs and even Electro Convulsive Therapy (ECT) goes towards the common pathway of raising the levels of amine transmitters with consequent down regulation of adrenergic receptors [13]. Hence an SSRI group of drugs by raising serotonin, may be decreasing the release of dopamine with correction of aggression and emotional quieting. Literature has also claimed about the high incidence of PD in patients on prolonged therapy with SSRI. Further, there is a possibility of EPS with therapeutic dose of all groups of antidepressants, whether on short or long term use, though they were more with duolexitine and few with escitalopram [14].

Still, we would like to reassess the literature and analyze them-

Evaluating the role of serotonin agonist drugs

Various research articles [5] have mentioned about the low levels of serotonin and norepinephrine in basal ganglion in PD patients. There are experimental evidences for the release of dopamine by serotonin nerve endings, but still no clear cut clinical improvement was seen in patients. Literature has further mentioned about the conversion of levodopa to dopamine in serotonin neurons as a compensatory measure in PD and subsequent release in response to stimulation by serotonin agonists [15-17]. However released dopamine from serotonin nerve endings following stimulation by agonists may be acting as false neurotransmitter [18].

Hence the low levels of serotonin observed in postmortem studies may be due to simultaneous senile degenerative changes of serotoninergic neurons too. Further there are indirect evidences for dopamine agonists like ergolines due to their additional serotonin agonist nature may be responsible for dyskinesias and possible psychotic features. The literature has further mentioned about the possibility of serotonin having role in tremor symptoms [19] which again indicates that serotonin neuronal hyper excitability may also be responsible for part of PD features other then dopamine and rather serotonin antagonist drugs may have a more significant role. Due to senile changes low levels of serotonin markers and up regulation of serotonin receptors are expected [20, 21]. As above $5HT2_{A/C}$ receptors hyper excitability is known to inhibit the direct (facilitator) pathways of dopamine system via GABA [12], corresponding to our results of atypical antipsychotic drugs by similar effects may favor the dopamine release to some extent for the help of PD.

Olanzapine may increase the levels of dopamine levels at basal ganglion too at sub therapeutic doses while at therapeutic antipsychotic dose few extra pyramidal symptoms may be seen due to simultaneous block of D_2 receptors. Literature has mentioned about the differential actions of olanzapine on D_2 and D_1 receptors [22], though our results favor enhance release of dopamine at sub antipsychotic doses of 0.5 mg/kg in mice.

Hence on current date instead of serotonin agonists, serotonin antagonistic drugs may probably have better outcomes as regards the improvement of PD. So further clinical trials have to be conducted to compare, the better efficacy of low dose olanzapine over the SSRI ones for the treatment of depression. Olanzapine has mild anti-cholinergic property which again may be responsible for low EPS in addition to probable dopamine release as suggested by us.

Regarding the use of ondansetron for EPS [6]

$5HT_3$ sub receptors are excitatory in the area postrema of the brain and responsible for nausea and vomiting. Thus serotonin antagonism through these receptors may also be enhancing the dopamine release or they may have an additional anticholinergic property to be helpful in catatonia.

Use of sarizotan

The serotonin drugs with pre synaptic $5HT_{1A}$ actions may actually decrease the release of not only serotonin, but also of other neurotransmitters like dopamine, etc. with the net utility for LID and also psychotic features associated with levodopa therapy, but may have the potential to worsen the PD features. We think of $5HT_{1A}$ actions, they may have a role in anxiety too, similar to buspirone and ipsapirone. The role of clozapine and mirtazapine to correct dyskinesias [23] in therapeutic doses can be explained due to their pre synaptic agonistic actions. For the same reason $5HT_{2A/C}$ inverse agonists (like pamivansarin) may favor direct pathways (enhanced dopamine release) to help patients of PD [24]. Currently it has U. S FDA approved status (2014) for treatment of Parkinsonism Disease Psychosis (PDP).

CONCLUSION

The olanzapine at low dose appears to have serotonin antagonism to enhance dopamine release property at basal ganglion through direct pathways to help PD patients. Similarly, at the same dose it may have partial D_1 agonist activity too. Though at therapeutic dose it has established D_2 antagonism in addition to being $5HT_{2A/C}$ antagonist. This enhanced dopamine may also be responsible for less frequency of EPS seen other than $5HT2s_{A/C}$ antagonism.

Still, some very useful conclusions from therapeutics point of view can be drawn due to overall inhibitory effects of serotonin on dopamine activity.

(i) $5HT_{1A}$ agonist drugs like sarizotan, buspirone and also clozapine too (due to additional pre synaptic actions) may be useful for LID and PDP, but higher doses may probably deteriorate the PD features due to dopamine inhibition.

(ii) Olanzapine, in low doses by block of $5HT_{2A/C}$ receptors may potentiate the actions of D_1 agonists for help of PD patients. While the therapeutic dose due to D_2 receptors block may produce EPS. Similar $5HT_{2A}$ inverse drugs like pamivanserin are under clinical trial for role PDP and we feel they may have also role in PD improvement too.

(iii) Ondansetron due to $5HT_3$ antagonism may improve dopamine levels to control EPS. This protection could also be due to its additional anticholinergic property too.

(iv) $5HT_4$ agonists like cisapride have a role in the gastrointestinal tract, hence may be useful for constipation secondary to PD.

(v) $5HT_5$ receptors are not found in human.

(vi) $5HT_{6,\ 7}$ antagonists may oppose the serotonin activity at basal ganglion to enhance dopamine levels. If designed in the future, they too may have potential for the help of PD patients. Further clinical trials will be needed to ascertain their utility.

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CONFLICT OF INTERESTS

Declared none

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