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EFFECTS OF TRYPTOPHAN AND VALINE ADMINISTRATION ON BEHAVIORAL PHARMACOLOGY OF HALOPERIDOL

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Development of antipsychotics with slight/no extra-pyramidal symptoms (EPS) and/or other side effects is one of the exploring fields of drug research. Haloperidol is a high potency typical neuroleptic used in the treatment of schizophrenia but produces muscles related side effects commonly known as EPS. These effects are not produced following the administration of atypical neuroleptics such as clozapine. A severe side effect of clozapine treatment is however, agranulocytosis. This involves investigation on the mechanism by which a typical neuroleptic acting via serotonergic mechanism tends to produce less or no EPS. The present study was, therefore, designed to determine the effect of serotonin precursor tryptophan and a large neutral amino acid other than tryptophan (valine) on the modulation of haloperidol induced catalepsy and akinesia. Cataleptic effects of the drug and activity reducing effects were monitored on inclined surface and in an activity box or open field respectively. The results are discussed in the context of a role of tryptophan and valine induced changes of brain serotonin in modifying the extrapyramidal and monoaminergic effects of the typical neuroleptic haloperidol. In the present study administration of TRP and valine decreased activity in rats, haloperidol-induced catalepsy' was not modulated by prior administration of tryptophan or valine. Brain serotonin levels were elevated by haloperidol treatment and correlated very well with the behavioral response. These findings suggest a possible serotonergic involvement in neuroleptic induced tardive dyskinesia and an amelioration of the disorder through TRP supplementation.

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INTRODUCTION

Schizophrenia

Schizophrenia is-a chronic severe mental illness affecting approximately 1-1.5% of the population (Beaver and Perry 1998, Wyatt *et al*., 1995) and leads to suicide in 10% of affected patients (Beaver and Perry, 1998). It appears first in adolescence or early adulthood and continuing throughout the person's life, interfering with all aspects of employment, home and family life (Rona *et al*., 1999). The disease is more common among the male gender and the condition has a uniform prevalence throughout the world. However, the prevalence in the elderly is 1%, of whom 10% show late onset of schizophrenia. Late onset is more common in women and is typically paranoid schizophrenia. Schizophrenia can be characterized by disturbances in the areas of brain responsible for thought, perception, attention, motor behavior, emotion and life functioning. The symptoms of the disease are divided into positive and negative. Negative symptoms have two different origins and referred to as primary and secondary negative symptoms. Symptoms that comprise behavioral deficits like blunting of emotions, language deficits and lack of energy are characterized as primary symptoms. Secondary negative symptoms are those that are secondary to psychosis, dysphoria and neuroleptic adverse reactions. Studies based on positron emission tomography (PET) reveal that schizophrenics with negative symptoms have reduced brain activity in the prefrontal cortex of the brain. Positive symptoms are not as disabling as the negative symptoms but are somewhat frightening, as they constitute hallucinations, delusions, and bizarre behavior (Russell J. Greene, 1993).

The DA hypothesis of schizophrenia proposes that brain DA synapses are overactive in schizophrenia. When drugs block DA receptors in the basal ganglia, the schizophrenic symptoms are reduced. Serotonin (5-hydroxytryptamine, 5-HT) is also implicated in the pathophysiology of schizophrenia, by result that parallel those implicating DA as a candidate for the same cause, particularly, the psychotogenic properties of serotonin agonists and antipsychotic properties of some serotonin antagonists (Seeman, 1992).

Haloperidol

Haloperidol is a high potency typical neuroleptic (David N. Osser, 1998). It is used in the treatment of schizophrenia. Typical neuroleptics occupy a traditional position in antipsychotic treatment. These medications block various DA receptors in the brain and limit psychosis. They produce the muscle-related side effects commonly known as the EPS (David N. Osser, 1998).

EPS and other adverse effects of haloperidol; atypical antipsychotics

Although neuroleptics have been widely prescribed for the treatment of schizophrenia since 1950's (Baldessarini 1985) there beneficial effects are accompanied by involuntary movement disorders. These neuromuscular extrapyramidal side effects (EPS) include akathisia, dystonia and Parkinsonism (Ayd, 1983) and the late appearing tardive dyskinesia (TD) (Klawans, 1985).

Dopamine

Dopamine (DA) is a biogenic amine synthesized in the hypothalamus, in the arcuate nucleus, the caudate and various areas of the central nervous system (Velasco and Luchsinger, 1998). DA is converted to dihydroxy-phenylacetic acid (DOPAC) by intraneuronal monoamine oxidase (MAO). DA is also converted to homovanillic acid (HVA) extraneuronally through the sequential action of catechol-0-methyl transferase (COMT) and MAO. Thus, DOPAC and HVA are the main metabolites of DA in the CNS (Cooper, 1991).

Serotonin

Serotonin, is widely distributed in animals and plants, occurring in vertebrates, fruits, nuts and venoms (Borne, 1994). 5-HT actions are terminated by its destruction via monoamine oxidases (MAO) (Young *et al*., 1980) that converts it to an intermediate product 5-hydroxyindole acetaldehyde (Beck *et al*., 1987). Most of this compound is oxidized through NAD' dependent aldehyde dehydrogenase into the principle urinary metabolites of 5-HT i.e. 5-hydroxyindole acetic acid (5-HIAA) (Burkhalter and Frick, 1987 and Haleem, 1990).

Large neutral amino acids

A reduction in the availability of TRP to the brain could be achieved by oral or parental administration of LNAAs competing with TRP for transport across the BBB (Rossi-Fanelli and Congiano, 1991). Several studies have reported that the presence of LNAAs in the plasma decreases the transport of TRP to the rat brain (Yuwiler *et al*., 1977; Bloxam *et al*., 1980). LNAAs decrease the conversion of TRP to 5-HT and further decrease the amount converted to its metabolite 5-HIAA by a common mechanism competition with TRP for transport out of the circulation into tissues where metabolism occurs (Curzon and Murphy, 1986). In rat models, it has been shown that a rise of 300% in the plasma TRP/LNAAs ratio leads to 80-90% increase in brain TRP (Leathwood, 1987).

A hypothesis explaining the receptor basis of the atypical neuroleptics is the serotonin-dopamine-antagonism (SDA) hypothesis. This hypothesis suggests that the blockade of serotonin 2A receptors in addition to DA D2 receptors help to prevent or minimize Parkinsonism (Huttunen 1995; Leysen *et al*., 1994; Meltzer 1989; Meltzer 1995; Meltzer *et al*., 1995; Meltzer *et al*., 1996 and Stockmeier *et al*., 1993). However, the relevance of serotonin 2A receptor blockade in the treatment of schizophrenia is controversial and not been confirmed (Nyberg & Farde, 1997 and Seeman *et al*., 1997).

The present study was designed to investigate the effect of tryptophan and valine administration on haloperidol induced behavioral and catalepsy. The findings will help to understand a role of serotonin in the precipitation of neuroleptics-induced catalepsy. The results will possibly suggest the role of serotonin (agonists/antagonists) as adjuncts for the treatment of extrapyramidal side effects of neuroleptics and will help in the development of atypical neuroleptics with fewer side effects.

MATERIALS AND METHODS

Animals

The study was carried out on locally bred male albino-Wistar rats weighing in the range of 200-250 gms, They were purchased from Agha Khan University (AKU). The rats were caged individually and kept in a peaceful environment. The cage floor was covered with sawdust. They were kept under a 12h light dark cycle at controlled (25^{o}C) temperature.

Drugs

TRP and valine of Merck (1 mg/ml of saline): 50 mg/kg IIP, haloperidol (serenace 5 mg/2 ml ampoule): 2.5 mg/kg I/P. The amino acids and haloperidol were injected in volume of 1 ml/kg body weight. Control animals received saline (0.9% NaCl) in volume of 1 ml/kg.

Experimental protocol

The study was carried out on thirty-six rats on six consecutive days. The study was designed in such a way that six rats were divided into two main groups A & B. Both groups consisted of three animal models. Animals of both groups were administered intra peritoneal (I/P) saline, tryptophan and valine as a first dose while second dose was followed by saline in group A and haloperidol in group B after one hour.

Monitoring of catalepsy and activity (open field activity)

An inclined surface was used to monitor catalepsy produce following the second dose. The animals were placed for two minutes on the inclined surface in such a way that they hold the surface with their fore paws. The time taken to move their neck was observed. The open field apparatus used in the experiment consisted of a transparent square area home cage. The method used was essentially as described earlier (Haleem *et al*., 1988) for both groups. Experiment was performed under white light and in a very quiet room to avoid any noise effect. After administration of second dose animals were placed in the square home cage. Square crossings, corner sittings and grooming were observed for ten minutes.

Statistical analysis

Mean values and standard deviation (± SD) were calculated by using MS Excel 95. Neurochemical/behavioral data on the effects of haloperidol on TRP and valine treated rats was subjected to two way ANOVA [factor 1 haloperidol, factor 2 amino acids (TRP and valine)]. Individual comparisons were made using Newman-Keuls statistics. Differences between various groups were considered statistically significant when $p<0.05$.

RESULT

Effect of tryptophan and valine pre administration on haloperidol induced catalepsy:

Fig.1 and table 1 show the effect of TRP and valine pretreatment on haloperidol induced catalepsy. Two-way anova showed significant effect of haloperidol ($F=26.7$ df 1,30 $p<0.01$). Effects of amino acid (TRP and valine) administration were not significant ($F=0.0023$ df 2,30 $p>0.05$). Interaction between haloperidol and amino acid was also insignificant ($F= 0.84$ df 2,30 $p>0.05$). Post hoc

Table 1

Effect of tryptophan and valine administration on haloperidol-induced catalepsy

Parameter	2nd inj saline			2nd inj haloperidol			Two way anova		
1st inj	Saline	TRP	Valine	Saline	TRP	Valine	F-Hal	F-AA	F-Inter
				*	*	*	df 1,30	df 2,30	df 2,30
	1.94	1.52	2.49	100	100	100	F=26.7	F=0.0023	F=0.848
Geotropism	± 1.72	± 1.33	±1.05	± 0	± 0	± 0	P<0.01	P>0.05	p>0.05

Values are means ± SD (n=6). Significant differences by Newman-Keuls test, * p <0.01 from rats given similar 1st inj and 2nd dose of saline injected rats following two way anova. Catalepsy (%):

Table 2

Effect of tryptophan and valine administration on haloperidol induced hypolocomotion

Parameter	2nd inj saline			2nd inj haloperidol			Two way anova		
1st inj	Saline	TRP	Valine	Saline	TRP	Valine	F-Hal	F-A.A	F-Inter
		+	+	*	*		df 1,30	df 2,30	df 2,30
Cage Crossing	47.16	24.33	25.16	5.83	5.83	11.33	F=50.24	F=7.44	F=13.08
	± 16.53	± 10.78	± 9.9	± 4.66	± 2.56	± 10.34	P<0.01	P<0.05	P<0.01

Values are means ± SD (n=6). Significant differences by Newman-Keels test, *p<0.01 from rats given similar 1st inj and 2nd inj of saline, + p<0.01 from respective saline (1st inj) injected rats following two way anova.

analysis by Newman-Keuls test showed that haloperidol administration produced comparable catalepsy in saline, TRP and valine preinjected rats.

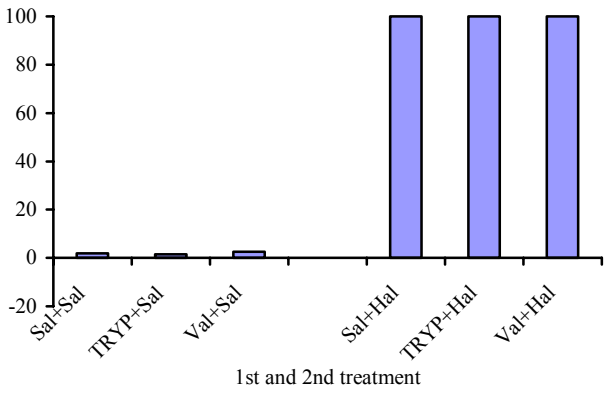

Fig. 1: Effect of tryptophan and valine administration on haloperidol induced catalepsy. Values are means + SD (n=6).

Effect of tryptophan and valine pre administration on haloperidol induced hypolocomotion

Fig 2 and table II shows the effect of haloperidol on the activity (cage crossing) of saline and amino acid injected rats. Two-way anova showed significant effect of haloperidol ($F= 52.24$, df 1,30 $p<0.01$), Effect of amino acid (TRP and valine) administration ($F=7.44$ df 2,30 $p<0.05$) and interaction between haloperidol and amino acid ($F= 30.08$ df 2,30 $p<0.01$) was also significant. Post hoc analysis by Newman-Keuls test showed that administration of TRP and valine decreased activity in rats given second injection of haloperidol. Haloperidol administration decreased cage crossing in saline and TRP injected rats but not in valine preinjected rats.

Cage Crossing

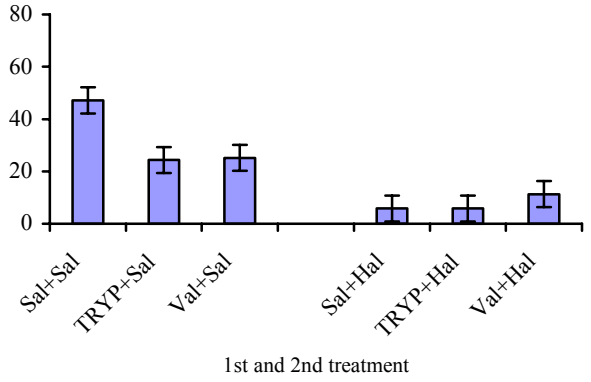

Fig. 2: Effect of tryptophan and valine administration on haloperidol induced hypolocomotion. Values are means + SD (n=6).

DISCUSSION

Effect of tryptophan and valine on activity

In the present study administration of TRP and valine decreased activity in rats. Tryptophan is the precursor of 5-HT and is supposed to increase brain serotonin functions. A role of 5-HT in the context of activity is evident in a number of studies.

It has been reported by Oberlander *et al* (1986) that RU 24969, a potent 5-HT1 agonist produces hyperlocomotion that was blocked by haloperidol and concluded that 5-HT1 receptors are involved in the motor execution of locomotion.

Moreover, Hoyer *et al*., 1994 has also reported that the 5-HT1B receptor agonist, RU24969 exhibits clear effects on locomotion and despite its poor selectivity for 5-HT1A receptors, the hyperlocomotion produced by RU 24969 can be antagonized by propanolol (Lucki, 1992). However, there is no dopaminergic link in the locomotor response to RU24969. Hyperactivity syndrome produced in rats by the injection of L-TRP along with monoamine oxidase inhibitor is also produced by the stimulation of postsynaptic 5-HT receptors (Heal *et al*., 1976) and this hyperactivity was also blocked by haloperidol (Heal *et al*., 1976). The inhibition is probably due to involvement of a dopaminergic system in the behavioral expression of 5-HT induced hyperactivity.

On the other hand, TRP administration alone decreases locomotor activity (Taylor, 1976; Stewart *et al*., 1976). Balsara *et al* (1979) reported that TRP decreased the intensity of amphetamine induced stereotypy. Furthermore, Baldessarini *et al* (1975) described that pretreatment with 5-HTP decreased apomorphine induced circling in rats with unilateral lesions of the nigrostriatal pathway. Kozell *et al* (1985) reported that an increase in dietary TRP significantly reduced the frequency of haloperidol induced head movements describes TD. Brain serotonin levels were elevated by haloperidol treatment and correlate well with the behavioral response. A decrease in activity in rats injected with tryptophan is therefore consistent with the activity reducing effects of serotonin. Possible mechanism by which valine could reduce activity is however, less clear.

Extrapyramidal effects of haloperidol

A number of studies have reported the induction of catalepsy by haloperidol in rats (Bartoszyk *et al*, 1996). The drug is known to be a potent cataleptogenic agent (Fregnan and Porta, 1981). Even low doses of haloperidol (0.25 mg/kg) can cause catalepsy (Bligh-Glover, 1995). Isoclozapine is at least three-fold more selective at 5-HT2A receptors than at D2 receptors yet it elicits considerable catalepsy at high doses (Seeman *et al*., 1997). Clozapine at a mean dose lower than 50 mg/day improves drug induced psychosis in PD without significant worsening of motor function, and the effect wears off once the treatment stops

(Pollak *et al*., 2004). Casey (1991; 1993) reported that antipsychotics that block both D2 and 5-HT2A receptors elicit Parkinsonism or catalepsy. Haloperidol induced catalepsy as observed in the present study is therefore explainable in terms of D2 antagonist activity of the drug.

Typical neuroleptics have been widely prescribed for the treatment of schizophrenia (Baldessarini, 1985) but a common and serious drawback of the conventional antipsychotics is their association with a range of motor disturbances (Barnes and McPhillips, 1998). High potency drugs e.g. haloperidol, the prototype of butyrophenone class are generally more associated with EPS (Schwartz and Brotman, 1992). These neuromuscular extrapyramidal side effects include akathisia, dystonia and Parkinsonism (Ayd, 1983) and the late appearing TD (Klawans, 1985). The parkinsonian syndrome is an undesirable neurologic side effect of the typical neuroleptics such as chlorpromazine and haloperidol (David N. Osser, 1998). Neuroleptic induced EPS is thought to be caused by the blockade of DA receptors in the nigrostriatal tract resulting in a relative increase in cholinergic activity (Glacer, 2000). Despite a role of serotonin in control motor activity, in the present study haloperidol-induced catalepsy was not modulated by prior administration of tryptophan or vatine.

Effects of tryptophan and valine on haloperidol induced extrapyramidal side effects

Various studies have been conducted with respect to TRP supplementation with haloperidol. Kozell *et al* (1987) studied the relationship of dietary manipulation of TRP and its effect on haloperidol induced TD. Increased dietary TRP (1 vs 0.3%) significantly reduced the frequency of drug induced head movements. Brain serotonin levels were elevated by haloperidol treatment and correlated very well with the behavioral response. These findings suggest a possible serotonergic involvement in neuroleptic induced tardive dyskinesia and an amelioration of the disorder through TRP supplementation.

Johnson *et al* (1992) administered a high dose (25mg/kg) of haloperidol twice over a 3-week interval in combination of a dietary TRP supplement. The combination of haloperidol plus TRP was found to cause a long lasting increase in spontaneous chewing movements. These observations are interpreted in the context of TRP supplementation to antipsychotic therapy.

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