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EFFECT OF CO ADMINISTRATION OF HALOPERIDOL AND LARGE NEUTRAL AMINO ACIDS (TRYPTOPHAN AND VALINE) ON RATS STRIATAL DOPAMINE, SEROTONIN AND THEIR METABOLISM

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ABSTRACT

Haloperidol is a high potency typical neuroleptic used in the treatment of schizophrenia. Administration of haloperidol produces muscles related side effects commonly known as extrapyramidal effects (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. Development of antipsychotics with little/ no EPS and/ or other side effects is one of the exploring fields of drug research. 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 is, therefore, designed to determine the effect of serotonin precursor tryptophan and a large neutral amino acid (valine) other than tryptophan on the modulation of neurochemical changes in the striatum. Neurochemical estimation were done by HPLC-EC. Present study showed that administration of tryptophan increased tryptophan, 5HT, 5HIAA and DA concentration in the striatum. DOPAC and HVA were not effected. Administration of valine increased DOPAC concentration in the striatum and did not alter tryptophan, 5HT, 5HIAA, DA and HVA concentration. Administration of the haloperidol increased HVA, 5HT and 5HIAA concentration. No effect was produced on tryptophan, DOPAC and DA levels. Valine administration followed by haloperidol injection did not alter striatal tryptophan, 5HT, DA, DOPAC and HVA concentration but decreased 5HIAA concentration. Administration of tryptophan followed by haloperidol injection increased tryptophan and 5HT concentrations and decreased DA levels. No effect was produced on 5HIAA, DOPAC and HVA concentrations.

Administration of TRP increased plasma and brain concentration as well as DA levels in the striatum. Administration of valine did not decrease striatal TRP concentration while Haloperidol increased striatal 5-HT and 5-HIAA concentrations and no change in DA levels after haloperidol administration. whereas prior injection of TRP that increased 5HT concentration did not alter haloperidol-induced DA turnover in the brain

INTRODUCTION

Schizophrenia is a chronic relapsing psychotic disorder affecting mainly thought and behavior. The predominant biochemical abnormality seems to be functional overactivity of certain

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dopaminergic pathways. Various studies on typical antipsychotics show that they did not produce a significant effect on brain serotonin and administration of such typical neuroleptics e.g. chlorpromazine, haloperidol are associated with precipitation of EPS (Seeman *et al.,* 1993). Their long-term administration also produces a potentially distressing and irreversible TD. On the other hand, atypical antipsychotics lack these adverse effects to a remarkable extent (Seeman *et al.,* 1993). They represent varying degrees of activity at the DA (D1, D3 and D4), serotonin (5HT2A, 5HT2C), histamine (H1), adrenergic (α1) and muscarinic receptors (Del D. Miller *et al.,* 2000). Thus, although it appears that the blockade of dopaminergic receptors is necessary to produce an antipsychotic effect, it is now recognized that other neurotransmitters such as serotonin, glutamate, norepinephrine, acetylcholine and gamma amino butyric acid (GABA) may have important roles in the pathophysiology and treatment of schizophrenia (Del D. Miller *et al.,* 2000). It has been shown that serotonin system exerts its effect via modulation of the activity of dopaminergic neurons (Kozell *et al.,* 1987; Sandyk *et al.,* 1988). Animal studies showed that increasing brain serotonin through dietary tryptophan reduced haloperidol induced head movements in rats (Kozell *et al.,* 1987). Clinical data revealed that an oral tryptophan supplement greatly reduced TD in several patients refractory to other treatments (Sandyk *et al.,* 1988).

Lesions of serotonin cell bodies in the raphe nuclei augmented apomorphine-induced locomotor behavior (Grabowska *et al.,* 1973), whereas, pretreatment with 5-HTP decreased apomorphine-induced circling in rats with unilateral lesions of the nigrostriatal pathway (Baldessarini *et al.,* 1975). Moreover, it was found that tryptophan decreased the intensity of amphetamine-induced stereotypy (Balsara *et al.,* 1979). In contrast, the administration of DA antagonists has been shown to elevate both serotonin levels (Kozell *et al.,* 1987) and turnover (Rastogi *et al.,* 1981). Collectively, these data indicate that compounds enhancing serotonergic function tend to diminish DA mediated behaviors, while manipulations that diminish serotonin activity augment DA mediated behaviors (Johnson, Wagner and Fischer 1991). There is increasing evidence that blockade of serotonin receptors is involved in the unique properties of the atypical antipsychotics and now, data from some studies suggest that poor response to atypical antipsychotics may be associated with polymorphism of serotonin receptors (Del D. Miller *et al.,* 2000). Serotonin antagonism is probably involved in the mediation of the relative decrease in expression of EPS among atypical agents in contrast to typical neuroleptics (Del D. Miller *et al.,* 2000). 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, Stockmeier *et al.,* 1993). However, the relevance of serotonin 2A receptor blockade in the treatment of schizophrenia is controversial and not been confirmed (Seeman *et al.,* 1997).

The present study is designed to investigate the effect of tryptophan and valine administration on haloperidol induced behavioral and neurochemical changes and the role of serotonin in haloperidol induced extrapyramidal effects. TRP and valine preinjection would be expected to increase and decrease respectively the serotonin metabolism in the brain. Effects of these manipulations are determined on haloperidol-induced catalepsy and DA and 5-HT metabolism. 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.

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). Schizophrenia can be characterized by disturbances in the areas of brain responsible for thought, perception, attention, motor behavior, emotion and life functioning.

Neuroleptics:

The term neuroleptic is a synonym for antipsychotic agent and refers to their effects that differ from classical central nervous system (CNS) depressants. These agents diminish conditional behavioral responses, selectively dampen neurophysiologic effects of peripheral stimuli on the forebrain, possess a limited ability to produce generalized sedation i.e. without the impairment of consciousness providing an anxiolytic and tension relieving effect. These drugs cause lack of initiative and interest in the environment, a limited rage of emotion, a reduction in confusion and agitation and normalization of psychomotor activity. Psychomotor inhibition is a specific depression of overall activity but not at the expense of consciousness. Dopamine receptor antagonists or neuroleptics are effective in blocking hallucinations, delusions and straightening out distorted thoughts which are the manifestations of schizophrenia (Seeman, 1995). These agents produce difficulty in movement often described as Parkinsonian like effects or extrapyramidal effects (EPS). There is a correlation between the ability of neuroleptics to bind to DA receptors and the dosage required improving schizophrenic symptoms in patients. PET could also directly observe this effect in living subjects (Sedvall and Farde, 1995). Neuroleptics block DA D2 receptors in direct relation to their clinical antipsychotic potencies (Seeman 1992, Seeman *et al.,* 1975).

EPS and other Adverse Effects of Typical; 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). Late appearing dystonias involving the neck and trunk region characterized by delayed onset of choreic or dystonic movements have been reported and recently have been referred to as "tardive dystonia" (Tarsy, 1983).

Clozapine is the prototype of atypical antipsychotics exhibiting low affinity for D2 receptors and high affinity for 5-HT2 receptors producing a high 5-HT/D2 ratio that is responsible for its improved efficacy and decreased rate of EPS (Meltzer *et al.,* 1991). In case of conventional antipsychotics, the antagonism of DA in the mesolimbic system relieves the positive symptoms of schizophrenia but at the same time, the blockade of transmission in the nigrostriatal system leads to EPS. Similarly for the SDAs, antagonism of DA in the mesolimbic system relieves the positive symptoms of schizophrenia, however, the DA (D2) blockade in the nigrostriatal system is inhibited by increased release of DA secondary to serotonin (5HT2) blockade in this area (Huttunen 1995). Moreover, serotonin (5HT2A) antagonism and reversal of the DA deficiency in the mesocortical tracts and mesolimbic tracts can result in improvement of the negative and positive symptoms of schizophrenia (Stahl 2000). Further, serotonin blockade prevents DA from increasing prolactin levels thereby relieving patients of the adverse effects of galctorrhea, amenorrhea and gynecomastia (Stahl 2000).

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 and Hospital (AKUH). 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 temperature. Both ceiling and exhaust fans were working continuously throughout the study for the purpose of adaptation of rats to the new environment.

Drugs:

TRP and valine: 50 mg/kg I/P
Haloperidol: 2.5 mg/kg I/P

Chemeicals:

All the chemicals used during experiment and assays were purchased from Sigma Chemical Company or Merck.

Tissue Sampling Technique:

Decapitation of rats was carried out by guillotine. The study was performed in a balanced design such that the control and drug treated rats were killed alternatively to avoid the order effect.

Brain Dissection Technique:

Brains were excised rapidly from the cranial cavity within 30 sec of decapitation. The skin enclosing the skull was cut along the midline and removed to have an access to the dorsal skull plates. The plates were split by introducing one half of a pair of scissors along the midline. The plates were twisted and turned out across the border to expose the brain. With the help of fine forceps, the membrane covering the brain was removed. The fresh brain was dipped in cold saline (0.9% w/v) and then placed on a glass plate with its dorsal side upward. Brain was placed with its ventral side up in the brain slicer and further brain regions were separated out as described by Haleem *et al.,* (1990). The brain was divided into three slices by the introduction of two transverse cuts just above and below the hypothalamic extremities, with the help of a thin, sharp stainless steel blade. The slices were placed on a petri dish kept on ice, moistened with 0.9% sodium chloride (saline). The desired brain regions were identified with the help of stereotaxic atlas (Paxions and Watson, 1982). Striatal punches of 2.5mm diameter were made bilaterally in slice number one, with the help of cannulae. From the second slice, hypothalamus was dissected out with the help of sharp scalpel and forcep. Rest of the brain was collected and the regions were then kept in plastic Eppendorf tubes and stored at low temperature (-70°C) until analyzed by HPLC-EC.

Neurochemical Estimation by Reversed Phase High Performance Liquid Chromatography with Electrochemical Detection (HPLC-EC):

Method used was essentially as described elsewhere (Haleem *et al.,* 1990; Haleem and Parveen, 1994).

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 $p<0.05$.

RESULTS

Effects of haloperidol on the levels of indoleamines in the striatum of tryptophan and valine injected rats.

Fig. 1 and Table 1 shows the effect of haloperidol on TRP, 5-HT and 5-HIAA concentrations in the striatum of saline and amino acid (TRP and valine) injected rats. Two way anova showed insignificant effect of haloperidol on TRP ($F=0.56$ df 1,30 $p>0.05$) and 5-HIAA ($F=0.39$ df 1,30 $p>0.05$) levels and significant effect on 5-HT ($F=59.13$ df 1,12 $p<0.01$) levels. Effects of amino acid (TRP and valine) administration were significant for TRP ($F=21.83$ df 2,30 $p<0.01$) and 5-HT ($F=10.18$ df 2,12 $p<0.01$) but insignificant for 5-HIAA ($F=2.29$ df 2,30 $p>0.05$). Interaction between haloperidol and amino acid was significant for TRP ($F=84.48$ df 2,30 $p<0.01$), 5-HT ($F=29.82$ df 2,12 $p<0.01$) and 5-HIAA ($F=78.01$ df 2,30 $p<0.01$).

Posthoc analysis by Newman-Keuls test showed that haloperidol administration did not alter TRP levels in saline, TRP and valine pre-injected rats. It did not alter 5-HT and 5-HIAA levels in valine pre-injected rats. It significantly increased 5-HT ($p<0.01$) and 5-HIAA ($p<0.01$) levels in saline and TRP pre-injected rats. Rats pre-injected with TRP and killed after 2nd injection of saline exhibited higher TRP, 5-HT and 5-HIAA ($p<0.01$) levels than rats pre-injected with saline and killed after 2nd injection of saline. Rats pre-injected with TRP and killed after 2nd injection of haloperidol exhibited higher TRP and 5-HT ($p<0.01$), but not 5-HIAA levels than rats pre-injected with saline and killed after 2nd injection of haloperidol. Rats pre-injected with valine and killed after 2nd injection of saline exhibited TRP, 5-HT and 5-HIAA levels comparable to rats pre-injected with saline and killed after 2nd injection of saline. Rats pre-injected with valine and killed after 2nd injection of haloperidol exhibited smaller ($p<0.01$) levels of 5-HIAA but not TRP and 5-HT than rats pre-injected with saline and killed after 2nd injection of haloperidol.

Effects of haloperidol on the levels of catecholamines in the striatum of tryptophan and valine injected rats.

Fig 2 and table 2 show the effects of haloperidol on DA, DOAPC and HVA concentrations in the striatum of saline and amino acid (TRP and valine) injected rats. Two way anova showed insignificant effect of haloperidol on DA ($F=2.6$ df 1,30 $p>0.05$) and DOPAC ($F=0.86$ df 1,30 $p>0.05$) and significant effect on HVA ($F=44.38$ df 1,30 $p<0.01$) levels. Effects of amino acid (TRP and valine) administration were insignificant for DA ($F=0.14$ df 2,30 $p>0.05$), DOPAC ($F=0.65$ df 2,30 $p>0.05$) and HVA ($F=0.21$ df 2,30 $p>0.05$). Interaction between haloperidol and amino acid was significant for DA ($F=20.4$ df 2,30 $p<0.01$) and DOPAC ($F=13.2$ df 2,30 $p<0.01$) and insignificant for HVA ($F=0.73$ df 2,30 $p>0.05$).

Posthoc analysis by Newman-Keuls test showed that haloperidol administration did not alter DOPAC levels in saline, TRP and valine pre-injected rats. It also did not alter DA levels in saline and valine pre-injected rats but decreased DA levels in TRP pre-injected rats. It significantly increased HVA ($p<0.01$) levels in saline, TRP and valine pre-injected rats. Rats pre-injected with TRP and killed after 2nd injection of saline exhibited DOPAC and HVA levels comparable to rats pre-injected with saline and killed after 2nd injection of saline. Rats pre-injected with TRP and killed after 2nd injection of haloperidol exhibited DOPAC and HVA levels comparable to rats pre-injected with TRP and killed after 2nd injection of haloperidol. Rats pre-injected with TRP and killed after 2nd injection of saline exhibited higher ($p<0.05$) DA levels than rats pre-injected with saline and killed after 2nd injection of saline. Rats pre-injected with TRP and killed after 2nd injection of haloperidol exhibited lower ($p<0.05$) DA levels than rats pre-injected with saline and killed after 2nd injection of haloperidol. Rats pre-injected with valine and killed after 2nd injection

of saline exhibited higher ($p<0.05$) DOPAC levels but comparable DA and HVA levels than rats pre-injected with saline and killed after 2nd injection of saline. Rats pre-injected with valine and TRP and killed after 2nd injection of haloperidol exhibited DOPAC levels comparable to rats pre-injected with saline and killed after 2nd injection of haloperidol. Rats pre-injected with TRP and valine and killed after 2nd injection of saline exhibited HVA levels comparable to rats pre-injected with saline and killed after 2nd injection of saline. Rats pre-injected with TRP and killed after 2nd injection of saline exhibited levels of DOPAC comparable to rats pre-injected with saline and killed after 2nd injection of saline.

DISCUSSION

Effects of Tryptophan and Valine on Straital 5-HT and Dopamine Metabolism:

Administration of TRP increased plasma and brain TRP concentration. Our study shows that administration of 50mg/kg TRP produced a rise in straital TRP concentration that is in accordance with previous studies. (Curzon, 1979; Fernstrom, 1977; Moja *et al.,* 1989; Young *et al.,* 1989 and Haleem, 1990). This leads to an increase in brain 5-HT synthesis. TRP administration increased 5-HT and 5-HIAA levels in the striatum. Study reported that a rise in brain TRP does play a role in 5-HT synthesis and also determines the ongoing rate of 5-HT synthesis (Jequier *et al.,* 1969; Haleem, 1990). Several studies have reported the precursor relationship of the amino acid L-TRP to serotonin synthesis (Curzon and Knott, 1977; Schaecter and Wurtman, 1989). The rate of brain serotonin synthesis varies with its precursor concentration (Eccleston *et al.,* 1965; Weber and Horita, 1965; Moir and Eccleston, 1968). Studies have also reported the increase in brain TRP concentration and 5-HT metabolism followed by injected TRP (Moir and Eccleston, 1968; Haleem, 1990; Haleem *et al.,* 1998; Holder and Huether, 1990; Westerink and DeVries, 1991). Bengtsson *et al.,* (1991) demonstrated that by increasing the TRP concentration to a level of saturation for TRP hydroxylation of 5-HT formation are, as expected, increased. In conditions of reduced brain TRP concentration, a decrease in striatal 5-HT and 5-HIAA can therefore be expected (Moja *et al.,* 1989). However, there may be no changes in serotonergic responses after TRP injection (Trulson, 1985; Green and Grahame-Smith, 1976; Wurtman, 1987). Increased 5-HT metabolism may not necessarily imply extra function because 5-HT may not be available to the functional receptor sites. Thus, peripheral TRP load increased serotonin release only after electrical stimulation (Sharp *et al.,* 1992) i.e. only in conditions of enhanced serotonergic neuronal activity (Haleem *et al.,* 1998).

TRP administration increased DA levels in the striatum. Increases of DA in the striatum following TRP administration in our study are consistent with the findings of Smith *et al.,* (1997) that the release of 5-HT (by fenfluramine) causes a rise in striatal DA. However, according to Kahn and Davidson (1993), 5-HT exerts an inhibitory effect on DA function. The functional significance of greater DA concentration only in the striatum remains unclear.

Administration of valine did not decrease striatal TRP concentration. Administration of valine had no effect on 5-HT and its metabolism. Although valine is a LNAA and various studies have reported that the presence of LNAAs other than tryptophan in the plasma decreases the transport of TRP to the rat brain (Yuwiler *et al.,* 1977; Bloxam *et al.,* 1980). It has been also shown that a rise of 300% in the plasma TRP/LNAAs ratio leads to 80-90% increase in brain TRP concentration (Leathwood, 1987). This study explains that although valine is expected to decrease the TRP transport to the striatum. The expected effect of valine on brain tryptophan concentration probably could occur at higher doses of valine.

Effects of Haloperidol on Brain 5-HT and Dopamine Metabolism:

Haloperidol increased striatal 5-HT and 5-HIAA concentrations. Increased levels of 5-HT and 5-HIAA in the striatum after haloperidol administration are in accordance with the studies of Kozell *et al.* (1987) who reported that the administration of DA antagonists elevate serotonin levels as well as its turnover (Rastogi *et al.,* 1981). Haloperidol administration did not alter striatal DA and DOPAC levels but increased striatal HVA.

Our study demonstrated no change in DA levels after haloperidol administration. A study by Johnson *et al.* (1992) has also reported that there was only slight decrease in DA levels after three hours of haloperidol administration, after which no decrease in DA level was noted. Haloperidol acts as antagonist at DA receptors (Burki et at, 1975; Baldessarini, 1985; Schotte *et al.,* 1993; Matsubara, 1993). This result in an increase in its metabolism as indicated by increased levels of HVA.

Accumulation of HVA in the brain can be used as an index of the functional activity of dopaminergic neurons in the brain (Cooper *et al.,* 1991). Kendler *et al.,* (1981) has reported a four-fold increase in HVA levels after haloperidol administration in the rat striatum. Hence, it can be concluded that DA was metabolized to HVA as is evident from the elevated HVA levels following haloperidol administration.

Also, autoreceptors play an important role in controlling the response of various DA projections to acute and chronic treatment with DA antagonists e.g. haloperidol as well as to DA agonists. It has been reported that acute treatment with haloperidol significantly enhances DA synthesis in the medial and central substantia nigra, whereas the lateral substantia nigra is unaffected. The failure of the lateral part of this region to respond to haloperidol may reflect an absence or diminished number of somatodendritic autoreceptors in this region.

Effects of Tryptophan and Valine Prior Administration on Haloperidol Induced Changes of 5-HT and Dopamine Metabolism:

Other authors have reported an increase in DA turnover following the administration of haloperidol (Baldessarini, 1985; Schotte *et al.,* 1993 and Matsubara, 1993). Our results are consistent with pervious reports. In addition, we observed that prior injection of TRP that increased 5HT concentration did not alter haloperidol-induced DA turnover in the brain.

Valine administration is supposed to decrease 5-HT concentration (Yuwiler *et al.,* 1977 and Bloxam *et al.,* 1980) by decreasing the TRP transport to the brain. The decrease was not significant in our study. But valine prior administration did not alter haloperidol induced DA turnover in the brain and striatum.

- TRP administration prior to haloperidol increased 5-HT levels in the striatum and decreased 5-HIAA levels. In comparison, in saline pre-injected rats, both 5-HT and 5-HIAA levels were found to be increase. The decrease observed in 5-HIAA levels in TRP pretreated rats remain unclear.
- DA levels were also decreased in the striatum in comparison to saline preinjected rats. The decreases of DA are also consistent with the previous studies that compounds (e.g. TRP in our study) that enhance serortonergic function lead to attenuation of DA mediated behaviors (Johnson *et al.,* 1992). Kahn and Davidson (1993) reported that 5-HT exerts an inhibitory effect on DA function. Moreover, apart from increasing the availability of TRP to the brain, the administration of TRP also increases the formation of other neuroactive metabolites and decreases the availability of tyrosine for catecholamine synthesis (Huether *et al.,* 1992).

Table 1
Effect of haloperidol on TRP, 5-HT and 5-HIAA concentrations in the striatum of saline and amino acid (TRP and Valine) injected rats

Parameter	2nd Inj. Saline			2nd Inj. Haloperidol			Two way ANOVA		
1st Inj.	Saline	Tryp	Valine	Saline	Tryp	Valine	F-Hal	F-AA	F-Inter
TRP	N.S.	+	N.S.	N.S.	N.S.	N.S.	df 1.30	df 2.30	df 2.30
	4.892	12.77	3.76	3.94	11.71	4.11	F=0.56	F=21.83	F=84.48
	1.28	3.79	0.8	1.14	3.27	0.969	p>0.05	P<0.01	p<0.01
5-HT	N.S.	+	N.S.	*	*+	N.S.	df 1.12	df 2.12	df 2.12
	205.61	512.97	355.95	666.32	980.98	557.35	F=59.13	F=10.18	F=29.82
	13.07	15.56	79.76	190.98	146.7	2.57	p<0.01	p<0.01	p<0.01
5-HIAA	N.S.	+	N.S.	*	*	+	df 1.30	df 2.30	df 2.30
	379.46	784.93	420.07	584.94	578.42	358.48	F=0.39	F=2.29	F=78.01
	91.05	134.56	75.32	72.53	112.4	98.04	p>0.05	p>0.05	p>0.01

Values are means ± SD for TRP and 5-HIAA (n=6) and for 5-HT (n=3). Significant differences by Newman=Keuls 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.

Table 2
Effect of haloperidol on DA, DOPAC and HVA concentrations in the striatum of saline and amino acid (TRP and Valine) injected rats

Parameter	2nd Inj. Saline			2nd Inj. Haloperidol			Two way ANOVA		
1st Inj.	Saline	Tryp	Valine	Saline	Tryp	Valine	F-Hal	F-AA	F-Inter
DA	N.S.	+	N.S.	N.S.	*+	N.S.	df 1.30	df 2.30	df 2.30
	2227.32	3091.2	2651.15	2745.65	1902.39	2559.16	F=2.6	F=0.14	F=20.4
	517.8	628.93	226.2	441.39	487.48	439.96	p>0.05	P<0.05	p<0.01
DOPAC	N.S.	+	+	N.S.	N.S.	N.S.	df 1.30	df 2.30	df 2.30
	4642.99	5716.64	7687.6	7274.64	5724.89	6545.88	F=0.86	F=0.65	F=13.2
	668.06	1011.64	1754.73	2199.35	1324.6	2090.48	p<0.05	p<0.05	p<0.01
HVA	N.S.	N.S.	N.S.	*	*	*	df 1.30	df 2.30	df 2.30
	402.19	525.27	580.9	1544.4	1333.25	1252.9	F=0.39	F=2.29	F=78.01
	109.56	100.9	144.1	298.72	341.61	350.29	p>0.05	p>0.05	p>0.01

Values are means ± SD (n=6). Significant differences by Newman=Keuls test, *p<0.01 from rats given similar 1st Inj. and 2nd Inj. of saline, + p<0.05 from respective saline (1st Inj.) injected rats following two way ANOVA.

Striatal Indoleamines

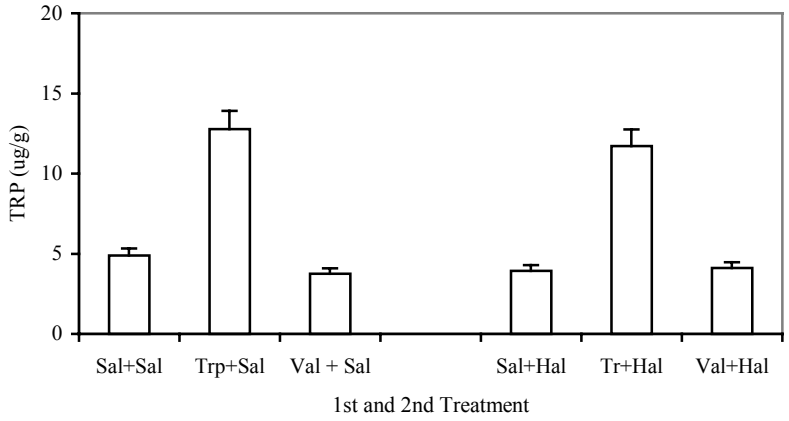

Fig. 1.1

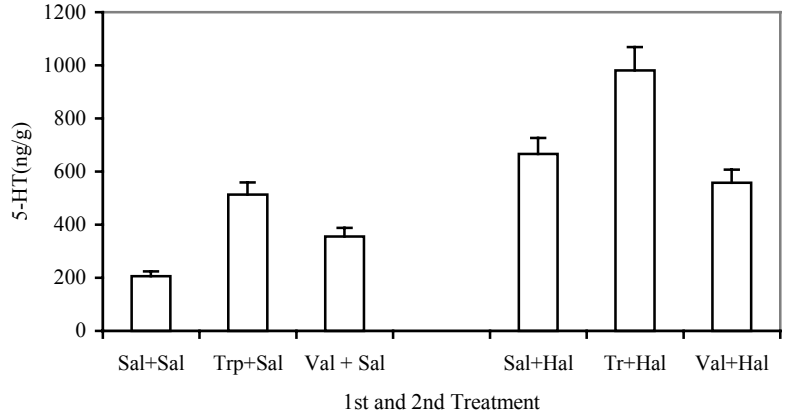

Fig. 1.2

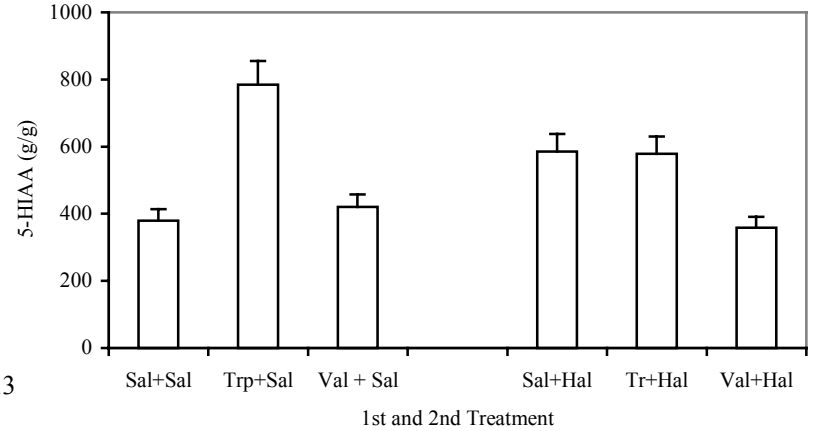

Fig. 1.3

Striatal Catecholamines

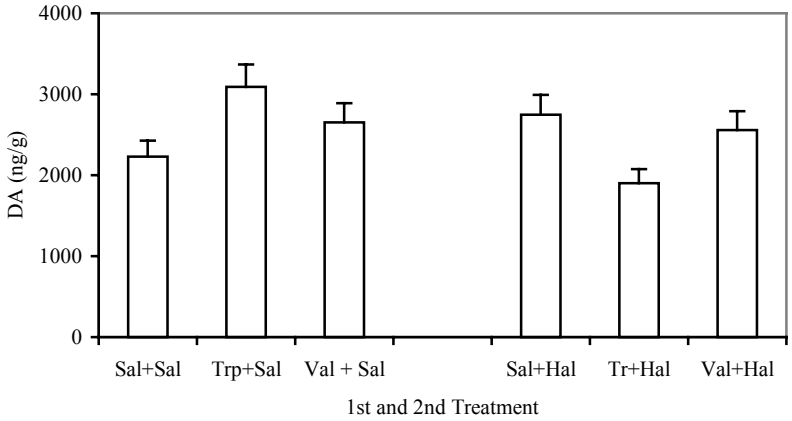

Fig. 2.1

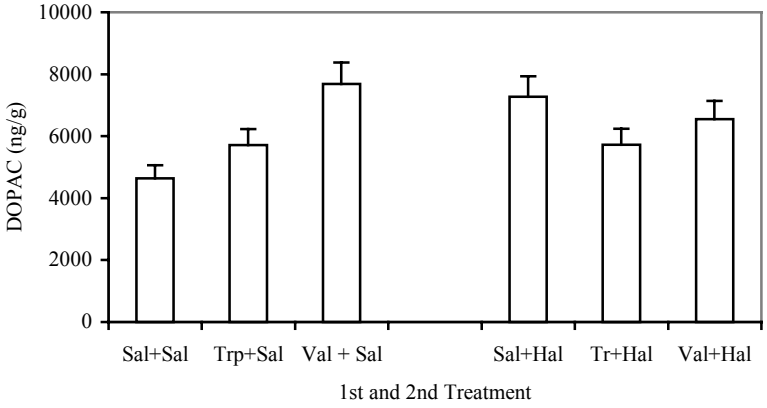

Fig. 2.2

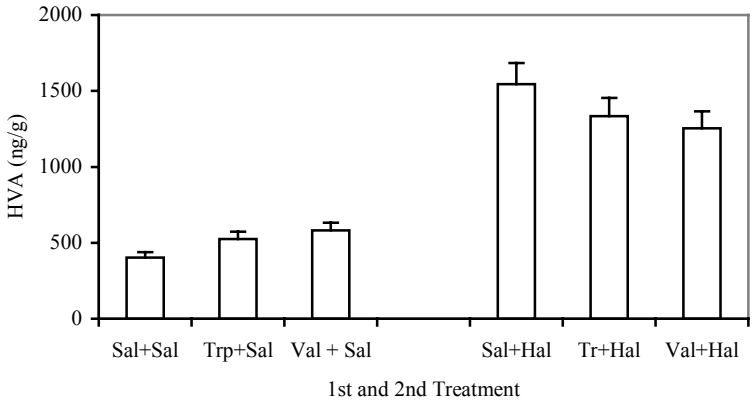

Fig. 2.3

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