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# Effect of Sodium Valproate pretreatment on Apomorphine and Dexamphetamine induced Stereotyped Behavior in rats.

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**Abstract**

Sodium valproate a broad spectrum antiepileptic elevates the brain GABA levels. Studies have suggested regulatory role of GABA on dopaminergic neurons, which is evident by behavioral studies in animals that reveal functional interaction between GABAergic and DAergic systems. Hyperfunctioning of DAergic system in rats is responsible for occurrence of stereotyped behavior (SB) in them. Drugs like apomorphine (Apo) and amphetamine induce SB by acting directly or indirectly. GABA, by acting at different sites has shown to influence the dopaminergically mediated behaviors. Hence the study was taken up to investigate the effect of sodium valproate pretreatment on apomorphine and dexamphetamine induced SB in rats. Pretreatment with 100 to 400mg/kg sodium valproate did not antagonize the apomorphine induced SB, however pretreatment with 100 to 400mg/kg sodium valproate significantly antagonized SB induced by 10 & 15mg/kg dexamphetamine.

**Keywords:** Sodium Valproate, Apomorphine, Dexamphetamine, Stereotyped Behavior.

## INTRODUCTION

Sodium valproate elevates the brain GABA levels and thereby enhances the GABAergic neurotransmission, [1] by stimulating the activity of the GABA synthetic enzymes and by inhibiting the GABA degradative enzymes.

Histological, electrophysiological and biochemical studies suggest a regulatory role of GABA on the dopaminergic (DAergic) neurons [2].Behavioral studies in animals have provided an additional evidence for a functional interaction between GABAergic and DAergic system. Drugs known to influence the central GABAergic systems have been reported to modulate the intensity of behaviors dependent on the functioning of the nigrostriatial and mesolimbic DAergic systems [3, 4].

Hyperfunctioning of nigrostriatal DAergic system in rats is responsible for occurrence of the stereotyped behavior (SB) of oral movement variety characterized by repetitive sniffing, gnawing, biting or licking behavior. Drugs like apomorphine and amphetamine induce SB either by acting directly or indirectly on the post synaptic striatal $D_2$DA receptors. Neuroleptics like haloperidol block the postsynaptic $D_2$DA receptors, and antagonize the SB induced by DA agonists [5].

GABA and GABA mimetic agents injected in pars compacta region of substantia nigra, exert a direct inhibitory influence on the functioning of the nigrostriatal DAergic neurons. However, when injected in pars reticulate they exert excitatory effect that is postulated to be due to inhibition of GABA and GABA mimetic agents or by inhibition of DA release.

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Thus GABA by acting at different sites in nigrostriatal and mesolimbic DAergic system can differently modulate the functioning of these systems.

Since it has been reported that the central GABAergic systems modulate the activity of nigrostriatal and mesolimbic DAergic systems and have shown to influence DAergically mediated behaviors the study was taken up to investigate the effect of sodium valproate pretreatment on the apomorphine and dexamphetamine induced SB in rats.

## MATERIALS AND METHODS

Albino rats of either sex, weighing between 100-180g, were used. They were allowed food and water ad libitum up to time of experimentation. Each animal was used only once. All observations were made between 10-17 hours at 27-30$^0$C in a noiseless, diffusely illuminated room. Each group consisted of 10 animals.

The drugs used were Sodium Valproate (Reckitt and Colman), Apomorphine hydrochloride (Sigma), Dexamphetamine sulphate (Koch Light), Haloperidol (Seranace injection, Searle). Haloperidol injection was diluted in distilled water. Apomorphine was dissolved in the distilled water containing 0.2mg/ml ascorbic acid while the remaining drugs were dissolved in distilled water only.

All drug solutions were prepared immediately before use and were injected intraperitoneally. The volume of injection was 5ml/kg body weight for valproate while for remaining drugs it was 2ml/kg body weight.

For observation of SB, the rats were placed in individual cages made of wire netting, measuring 30x20x20 cm, 30 min before drug treatment to allow adaptation to the new environment.

The intensity of SB was assessed over a 30 sec observation period at 10 min interval throughout its duration using the system of Costall and Naylor [6], where, periodic sniffing= score 1, continuous sniffing =2, periodic biting ,gnawing or licking=3, and continuous biting ,gnawing or licking=4. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the

group.

Sodium valproate and haloperidol were injected 1hr before apomorphine or dexamphetamine. The control groups received requisite volume of normal saline (NS) ip, 1hr before receiving apomorphine or dexamphetamine. Sodium valproate was tested in the dose range of 50 to 400mg/kg while haloperidol was tested in the dose of 0.5mg/kg.

The study was undertaken at Krishna institute of Medical Sciences, Karad. Maharashtra. All the procedures were performed in accordance with CPCSEA guidelines & the study was carried on following the approval of IAEC (Institutional animal ethical committee)

## STATISTICAL ANALYSIS

The results were statistically analyzed by the students unpaired t-test with the differences considered significant at $p<0.05$.

## OBSERVATIONS AND RESULTS

Sodium valproate (50 to 400mg/kg) did not induce SB in rats. Apomorphine (0.5 and 1mg/kg) induced dose dependent SB in rats (Table -1). Pretreatment with sodium valproate (50 to 400mg/kg) did not significantly influence apomorphine induced SB. However, pretreatment with 0.5 mg/kg haloperidol abolished SB induced by 0.5 and 1mg/kg apomorphine (Table-1)

Table 1.Effect of Sodium Valproate (VAL) and Haloperidol (HAL) pretreatment on Apomorphine (Apo) induced SB in rats.

| Study | | Treatment dose mg/kg | Intensity score Mean ±SEM |
|---|---|---|---|
| I A | 1 | NS + Apo 0.5 | 1.2 ± 0.13 |
| | 2 | VAL 50 + Apo 0.5 | 1.3 ± 0.15 |
| | 3 | VAL 100 + Apo 0.5 | 1.0 ± 0.00 |
| | 4 | VAL 150 + Apo 0.5 | 1.1 ± 0.10 |
| | 5 | VAL 200 + Apo 0.5 | 1.2 ± 0.13 |
| | 6 | VAL 300 + Apo 0.5 | 1.0 ± 0.00 |
| | 7 | VAL 400 + Apo 0.5 | 1.1 ± 0.10 |
| I B | 1 | NS + Apo 0.5 | 1.2 ± 0.13 |
| | 2 | HAL 0.5 + Apo 0.5 | 0.0 |
| IIA | 1 | NS + Apo 1 | 2.1 ± 0.10 |
| | 2 | VAL 50 + Apo1 | 2.2 ± 0.13 |
| | 3 | VAL 100 + Apo1 | 2.1 ± 0.10 |
| | 4 | VAL 150 + Apo 1 | 2.0 ± 0.00 |
| | 5 | VAL 200 + Apo 1 | 2.2 ± 0.13 |
| | 6 | VAL 300 + Apo 1 | 2.3 ± 0.15 |
| | 7 | VAL 400 + Apo 1 | 2.1 ± 0.10 |
| IIB | 1 | NS + Apo 1 | 2.2 ± 0.13 |
| | 2 | HAL 0.5 + Apo 1 | 0.0 |

NS= Normal Saline (5ml/kg ip for valproate control groups and 2ml/kg ip for haloperidol control groups).

Similarly, dexamphetamine (10 and 15mg/kg) induced dose dependent SB in rats (Table-2). Pretreatment with 50mg/kg sodium valproate did not significantly influence SB induced by 10 and 15mg/kg dexamphetamine. However pretreatment with 100 to 400mg/kg sodium valproate significantly antagonized the SB induced by 10 and 15mg/kg dexamphetamine. Pretreatment with 0.5mg/kg haloperidol abolished the SB induced by 10 and 15mg/kg dexamphetamine. (Table-2)

Table 2. Effect of Sodium Valproate (VAL) and Haloperidol (HAL) pretreatment on Dexamphetamine (DAM) induced SB in rats.

| Study | | Treatment dose mg/kg | Intensity score Mean ± SEM |
|---|---|---|---|
| IA | 1 | NS + DAM 10 | 3.0 ± 0.00 |
| | 2 | VAL 50 + DAM 10 | 2.8 ± 0.13 |
| | 3 | VAL 100 + DAM 10 | 2.4 ± 0.16* |
| | 4 | VAL 150 + DAM 10 | 2.0 ± 0.12** |
| | 5 | VAL 200 + DAM 10 | 1.2 ± 0.13*** |
| | 6 | VAL 300 + DAM 10 | 0.5 ± 0.16*** |
| IB | 1 | NS + DAM 10 | 3.0 ± 0.10 |
| | 2 | HAL 0.5 + DAM 10 | 0.0 |
| IIA | 1 | NS + DAM 15 | 3.9 ± 0.10 |
| | 2 | VAL 50 + DAM 15 | 3.7 ± 0.15 |
| | 3 | VAL 100 + DAM 15 | 3.3 ± 0.15* |
| | 4 | VAL 150 + DAM15 | 2.9 ± 0.10** |
| | 5 | VAL 200 + DAM 15 | 2.1 ± 0.10*** |
| | 6 | VAL 300 + DAM 15 | 1.4 ± 0.16*** |
| | 7 | VAL 400 + DAM 15 | 0.7 ± 0.15*** |
| IIB | 1 | NS + DAM 15 | 4.0 ± 0.00 |
| | 2 | HAL 0.5 + DAM 15 | 0.0 |

*p<0.05, **p<0.01, ***p <0.001.
NS= Normal saline (5ml/kg ip for valproate control groups and 2ml/kg ip for Haloperidol control groups)

## SUMMARY AND CONCLUSIONS

Behavioral studies in animals have demonstrated that drugs which influence the activity of central GABAergic system modulate the intensity of behaviors on the functional status of nigrostriatal and mesolimbic DAergic systems. Histological studies have demonstrated an anatomical connection between the central serotonergic and dopamiergic pathway [7, 8].Behavioral studies have shown that 5HT inhibits the synthesis and release of DA from rat brain by stimulating 5HT receptors. Since the 5HT induced inhibition

of DA release is blocked by $5HT_2$ receptor antagonists [9].With present study it was evident that pretreatment with 100,150,200,300 and 400mg/kg of sodium valproate, did not induce catalepsy nor antagonized the apomorphine induced SB in rats, it indicates that valproate at these doses does not block the post synaptic striatal D2DA receptors. However, pretreatment with 0.5mg/kg haloperidol abolished the SB induced by 0.5 & 1mg/kg apomorphine. (Table-1)

The antagonism of dexamphetamine SB by valproate (Table-2) is explained as follows. Dexamphetamine induce SB of the oral movement variety, by releasing DA from the nigrostriatal DAergic neurons with resultant stimulation of post synaptic striatal D2DA receptors by the released DA [10]. The intensity of dexamphetamine SB depends upon the availability of the intraneuronal stores of DA for release by dexamphetamine.

Benzodiazepines, which enhance GABAergic transmission at $GABA_A$ receptor site, have been reported to potentiate the DA dependent SB induced by methamphetamine in rats [11].

Pretreatment with 5HT precursors (5- Hydroxytrytophan, L-tryptophan) antagonized, while pretreatment with methysergide a 5HT antagonist and p-chlorophenylalanine (PCPA), a 5HT depletor, potentiated amphetamine stereotype behavior [12].

GABA-T inhibitor amino-oxyaceticacid (AOAA) elevates the brain GABA levels and thereby inhibit DA turnover (decreases the synthesis and release of DA). Similarly intraventricular or intranigral injection of GABA-T inhibitor ethanolamine-o-sulphate (EOS) also results in a decreased levels of DA metabolite 3-methoxy tyramine (3-MT), indicating that GABA decreases the release of DA from the nigrostriatal DAergic neurons [13]. Like GABA, 5-HT has also been reported to inhibit synthesis and release of DA from the nigrostriatal DAergic neurons [14].

Based on the findings we postulate that, valproate at 100 and 150mg/kg doses, by elevating the brain GABA levels and at 200, 300 and 400mg/kg doses, additionally by releasing 5-HT exerts inhibitory effect on nigrostriatal DAergic neurons and decreases the synthesis of DA in the nigrostriatal DAergic neurons. As a consequence the intraneuronal stores of DA decrease and less amount of DA is therefore available for release by dexamphetamine with resultant antagonism of dexamphetamine SB by valproate pretreatment.

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## REFERENCES

[1] Davis R, Peters DH, MC Tavish D. 1994. Valproic acid; a reappraisal of its pharmacological properties and clinical efficacy in epilepsy. *Drugs*, 47,332.

[2] Bartholini G, Stadler H. 1975. In: "Chemical tools in catecholamine turnover", p 235, (Almgren O, Carlson A, Engel J, Eds) Amsterdam, North Holland.

[3] Worms P, Willigens MT, Lloyd KG.1978."GABA involvement in neuroleptic catalepsy": *J Pharm Pharmacol*, 30; 716-718.

[4] Decsi L, Nagy J. 1988. Independent gabaergic and cholinergic modulation of apomorphine induced stereotyped raring in the rats. *Neuropharmacology*. 27(3); 281-5.

[5] Seeman P. 1980. Brain Dopamine Receptors. *Pharmacol Rev.,* 32,229-313.

[6] Costall B, Naylor RJ. 1974. Mesolimbic involvement with behavioral effect indicating antipsychotic activity: *Eur J Pharmacol,* 27, p 46.

[7] Writshafter D, Startford TR, Asin KE. 1987. Neurosci Lett, Evidence that serotonergic projections to the substantia nigra in the rat arise in the dorsal, but not the median raphe nucleus. 77,261-266.

[8] Rajda F, Laporte AM, Daval G, Verge D, Gozlan H, Hamon M. 1991. Neurochem Int, Autoradiography of serotonin receptor subtypes in the central nervous system. 18, 1-15.

[9] Muramatsu M, Tamaki-Ohashi J, Usuki C, Araki H, and Chaki S, Aihara H. 1988. 5 HT2 antagonists and minaprine block the 5HT induced inhibition of dopamine release from rat brain striatal slices. *Eur J Pharmachol.,* 153(1), 89-95.

[10] Seiden LS, Sabol KE, Ricaurte GA.1993. Amphetamine: effects on catecholamine systems and behavior. *Annu Rev Pharmacol Toxicol.,* 33, 639-677.

[11] Babbini M, Montanaro N, Strocchi P, Gaiardi M. 1971. Enhancement of amphetamine induced stereotyped behavior by benzodiazepines. *Eur J Pharmacol.,* 13,330-340.

[12] Balsara JJ, Jadhav JH, Muley MP, Chandorkar AG. 1979. Effect of drugs influencing central serotonergic mechanisms methamphetamine induced stereotyped behavior in rats. *Psychopharmacology,* 64,303-307.

[13] Racagni G , Bruno F , Cattabeni F, Maggi A, Di Giulio AM, Parenti M, Groppetti A. 1977. Functional interaction between rat substantia nigra and striatum; GABA and Dopamine interrelation. *Brain Res.,* 134,353-358.

[14] Meltzer HY, Nash JF.1991. Effects of antipsychotic drugs on serotonin receptors. *Pharmacol Rev*., 43,587-604.