

# Effect of Sodium Valproate pretreatment on Haloperidol induced catalepsy in rats.

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## Abstract

*Sodium valproate a broad spectrum antiepileptic, elevates the brain GABA levels. Studies have suggested a regulatory role of GABA on Dopaminergic neurons. Behavioural studies in animals have provided additional interaction between GABAergic and DAergic systems. Hypofunctioning of nigrostriatal DAergic system in rats is responsible for induction of catalepsy. Haloperidol induces catalepsy in rats by blocking post synaptic striatal D2DA receptors. Hence the study was taken up to evaluate the effect of sodium valproate pretreatment on Haloperidol induced catalepsy. Sodium valproate 100 to 400 mg/Kg significantly increased the cataleptic effect of Haloperidol at both 1 and 2 hour testing time intervals.*

**Key Words:** *Sodium valproate, Haloperidol, catalepsy*

## Introduction :

Sodium valproate is a broad spectrum anti-epileptic drug. It elevates the brain levels of the inhibitory neurotransmitter GABA, by stimulating the activity of the gamma aminobutyric acid (GABA) synthetic enzyme, glutamic acid decarboxylase (GAD) and by inhibiting GABA degradative enzymes, GABA transaminase (GABA-T) and succinic semialdehyde dehydrogenase (SSADH). It has been reported to enhance the postsynaptic responses to GABA by facilitating the electrophysiological effects and by blocking the neuronal uptake of GABA. Further, valproate has been suggested to enhance GABAergic neurotransmission by directly interacting with the picrotoxin-sensitive recognition site at GABA – benzodiazepine / chloride channel receptor complex. Histological, electrophysiological and biochemical studies suggest a regulatory role of GABA on the dopaminergic (DAergic) neurons<sup>[1]</sup>. The striato-nigral GABAergic pathway is believed to exert an inhibitory feedback controlling influence on the nigrostriatal DAergic neurons at the level of dopamine cell bodies or dendrites in the substantia nigra. The GABAergic

accumbens-tegmental pathway is postulated to modulate the activity of the mesolimbic DAergic pathway. Behavioural studies in animals have provided additional evidence for a functional interaction between the cited GABAergic and DAergic systems.

Drugs known to influence the activity of the central GABAergic systems have been reported to modulate the intensity of the behaviour dependent on the functioning of the nigrostriatal DAergic systems and the mesolimbic DAergic system<sup>[2]</sup>. Also GABAA and GABAB receptor agonists and antagonists have been shown to influence the DAergically mediated behaviours. Hence the study was taken up to evaluate the “Effect of sodium valproate pretreatment on haloperidol induced catalepsy in rats”.

## Materials and Methods

The protocol of the study was approved by the Institutional Animal Ethics Committee. Albino rats of either sex, weighing between 100-180 g, were used. They were allowed food and water ad libitum. Each animal was used only once. All observations were made between 10-17 hours at 37°C in a noiseless, diffusely illuminated room. Each group consisted of 10 animals.

The animals were placed in individual perspex cages (30x20x20) and were allowed for adaptation to the

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new environment. Animals were tested for catalepsy according to the method of Costall and Naylor<sup>[6]</sup> by placing both front limbs of the animal over an 8 cm high wooden block and measuring the time that the animals maintained this posture. The animals were considered cataleptic if they maintained this imposed posture for more than 10 secs.

Animals were tested for catalepsy at 0.5, 1, 2, 3 and 4 hours after treatment with sodium valproate (50 to 400 mg/kg), haloperidol (1mg/kg) and normal saline (5ml/kg body weight ip, control group).

Sodium valproate was injected one hour before haloperidol. Cataleptic scoring scheme modified from that of Costall and Naylor was as follows: Maintaining the cataleptic posture for 0-10 sec (0); 10-30 sec (1); 30-60 sec (2) ; 1-2 min (3) ; 2 min and more<sup>[4]</sup>.

Animals were tested for catalepsy at 1 and 2 hours after haloperidol treatment. Catalepsy score of each animal in the group was taken to compute the mean value of the group. The results were statistically analysed by the students unpaired t-test with differences considered significant at  $p < 0.05$ .

### Observations and Results

Treatment dose mg/kg		Catalepsy score at 1 hour (Mean + SE)	Catalepsy score at 2 hour (Mean + SE)
1.	NS + HAL 0.5	1.0 ± 0.00	0.8 ± 0.13
2.	VAL 50 + HAL 0.5	1.1 + 0.10	0.9 + 0.10
3.	VAL 100 + HAL 0.5	1.6 ± 0.16*	1.4 ± 0.16*
4.	VAL 150 + HAL 0.5	1.9 + 0.10**	1.7 + 0.15**
5.	VAL 200 + HAL 0.5	2.2 + 0.13***	2.0 + 0.00***
6.	VAL 300 + HAL 0.5	2.4 ± 0.16***	2.2 ± 0.13***
7.	VAL 400+ HAL 0.5	2.6 ± 0.16***	2.4 ± 0.16***

**Table 1: Effect of Valproate on haloperidol induced catalepsy (0.5mg/kg)**

1.	NS + HAL 1	2.8 + 0.13	2.6 + 0.14
2.	VAL 50 + HAL 1	2.9 + 0.10	2.7 + 0.15
3.	VAL 100 + HAL 1	3.4 ± 0.16*	3.2 ± 0.3*
4.	VAL 150 + HAL	3.7 ± 0.13**	3.5 ± 0.16**
5.	VAL 200 + HAL 1	4.0 + 0.00***	3.8 + 0.13***

\*P < 0.05, \*\* P < 0.01, \*\*\* P < 0.001 NS = Normal saline (5ml/kg ip).

**Table 2: Effect of Valproate on haloperidol induced catalepsy (1mg/kg)**

Preliminary studies with sodium valproate (50 to 400 mg/kg) did not induce catalepsy in rats. Haloperidol (0.5 and 1 mg/kg) induced dose dependent degree of catalepsy in rats at both 1 and 2 hour testing time intervals (Table 1).

Pretreatment with 50 mg/kg sodium valproate did not significantly affect the cataleptic effect of haloperidol (0.5 and 1 mg/kg) at both 1 and 2 hour

testing time intervals. However pretreatment with 100 to 400 mg/kg sodium valproate significantly increased the cataleptic effect of haloperidol (0.5 mg/kg) at both 1 and 2 hour testing time intervals (Table 1). Similarly, pretreatment with 100, 150 and 200 mg/kg sodium valproate significantly enhanced the cataleptic effect of 1 mg/kg haloperidol at both 1 and 2 hours testing time intervals (Table 2).

The effect of pretreatment with 300 and 400 mg/kg sodium valproate on 1 mg /kg haloperidol induced catalepsy was not studied since pretreatment with 200 mg/kg dose of sodium valproate had maximally potentiated the cataleptic effect of 1 mg/kg haloperidol (Table 2).

### Discussion

Catalepsy is defined as a state of failure to correct the externally imposed posture. Hypofunctioning of the nigrostriatal DAergic system in the rat with resultant functional lack of DA at the post synaptic striatal D2 DA receptors, is responsible for induction of catalepsy. Neuroleptics, eg haloperidol induce catalepsy in the rats by blocking the post synaptic striatal D2 DA receptors<sup>[7]</sup>. GABA is present as a major neurotransmitter in all of the major efferent pathways, related to the nigrostriatal and the mesolimbic DAergic systems.

It is evident with biochemical, electrophysiological and behavioral studies that GABA and GABA mimetic agents have complex influence on the functioning of the nigrostriatal and mesolimbic DAergic systems. Biochemical studies have demonstrated that GABA – T inhibitor amino-oxyacetic acid (AOAA) inhibits DA turnover both in the striatum and the limbic system<sup>[8]</sup> and also inhibits the increase of striatal homovanillic acid (HVA) content induced by chlorpromazine<sup>[9]</sup> and haloperidol<sup>[10]</sup>.

It has been reported that pretreatment with AOAA and baclofen potentiated haloperidol induced catalepsy in rats<sup>[11]</sup>. Similarly, benzodiazepines muscimol, AOAA and diaminobutyric acid (DABA an inhibitor of GABA uptake) potentiated catalepsy induced by haloperidol (0.3 and 0.6 mg/kg ip)<sup>[12]</sup>. Potentiation of haloperidol catalepsy by muscimol, AOAA and DABA is due to elevated GABA levels, which stimulated the GABA receptors located on cell bodies of nigrostriatal DA ergic neurons, thereby decreasing the release of DA into the synaptic cleft.

Further, Valproate (200, 300 and 400 mg/kg ), through the released 5-HT also inhibit the synthesis of DA and

hence decrease the stores of DA in the nigrostriatal DAergic neurons and thus makes less DA available for release during the neuroleptic compensatory “feedback” increase of nigrostriatal DAergic neuronal activity. As a result the haloperidol induced blockade of post synaptic striatal D2 DA receptors is counteracted to a lesser extent with resultant potentiation of haloperidol catalepsy in rats.

From the above observations it can be concluded that valproate potentiates haloperidol induced catalepsy in dose dependant manner. The potentiation has also been with both the doses of haloperidol. Since valproate is known to increase the GABA levels by various mechanisms, it is likely that the potentiation in cataleptic score could be associated with increased GABA level. This needs to be confirmed by measuring GABA levels and DA levels at various sites in brain of rats.

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