

## Experimental Evaluation of some central nervous system activities of Calcium Channel Blockers: Effect on isolation Combativeness and Suppression of Conditioned Avoidance Response

Chitra Singh<sup>\*1</sup> and Madhu Singh<sup>2</sup>

<sup>1</sup>Ph.d Scholar, Department of Pharmacology, BHU, Varanasi

<sup>2</sup>Assistant Professor, Bundelkhand Govt. Ayurvedic College, Jhansi

Corresponding author\*: [singh11chits@gmail.com](mailto:singh11chits@gmail.com)

### Abstract

The present study was designed to investigate effect of some Calcium Channel Blockers on Central Nervous System activities in terms of Isolation Combativeness and Suppression of Conditioned Avoidance Response. This present study was carried out over three different classes of CCB's, namely Benzothiazipine, Dihydropyridine and Piperazine, to evaluate their control activities on Central Nervous System. For this purpose Diazepam served as control. All the above tests were carried out over Albino Rats. In case of isolation combativeness Diltiazem in all three doses viz.; 5mg/kg, 10mg/kg, 20mg/kg and Flunarizine and Nifedipine in a dose of 20mg/kg, 10mg/kg respectively effectively calm down the animals. During screening of conditioned avoidance response; Diltiazem was effective in all the three doses viz. 5mg/kg, 10mg/kg, 20mg/kg. While Flunarizine and Nifedipine, were partly effective. Calcium channel blockers: Diltiazem, Flunarizine, Nifedipine in different doses: can affect central nervous system functions in different ways and can interact with some other drugs effective on central nervous system.

**Key words:** CCBs, isolation combativeness, conditioned avoidance response, diltiazem, nifedipine, Flunarizine, diazepam, aggressiveness, learning, memory

### 1. Introduction

Calcium channel blockers are widely used in the treatment of cardiovascular disorders for their actions on the voltage sensitive calcium channels in cardiac and smooth muscles<sup>1</sup>. The reorganization on calcium channel antagonist binding sites in the limbic regions of the brain<sup>2</sup>, raises the hope that these might also be helpful in some behavioural disorders<sup>3</sup>. Calcium channel blockers act by blocking one more type of calcium channel located in the cells. An interesting finding noted is that blocking of voltage gated channels results in antinociception. Voltage gated T, N, L type of calcium channel blockers contribute significantly to excitability of sensory neurons but the N channels are particularly important because they control release of neurotransmitters from the peripheral and central terminals. Recent studies provided a link between opioids system and calcium channels.

Golestein<sup>4</sup> reported the beneficial effects of Verapamil in panic disorders. However the clinical and experimental evidence for central nervous system effects of calcium channel blockers is little and variable with the test procedures as well with classes of calcium channel blockers. The main use of calcium channel blockers is in the management of various cardio vascular conditions like angina pectoris, hypertension, cardiac arrhythmias etc. Recent thoughts provoking studies have disclosed many facts of actions of calcium channel blockers on central nervous system<sup>5</sup>. Calcium channel blockers are supposed to be present in all the systems of our body and their blockade certainly effect the function of this system in all the ways. As far as their cardiovascular activities are concerned these are well documented but their effects on other system still remain unexplored. Of course there are some literatures about analgesic<sup>6</sup>, anticonvulsant<sup>7</sup>, and anxiolytic activities<sup>8</sup>. These studies have shown entire new aspect of this group of drugs. In recent years considerable attention has been focused on role of calcium channel blockers in modification of central nervous system activities. Keeping in mind, studies related to central nervous system effects of calcium channel blockers, present study has been formulated to elucidate neuroleptic activities like suppression of conditioned avoidance response and suppression of isolation combativeness.

As reported by Srivastava (1992)<sup>9</sup> calcium channel blockers, Verapamil, Diltiazem and Nifedipine significantly reduced fighting episodes induced by foot aggression. They also reported that Diltiazem and Nifedipine block Amphetamine as well as foot shock aggression. While Verapamil block both Amphetamine and Physostigmine. These

findings suggest that calcium channel blockers possess anti aggressive activity which may be attributed to decrease in central dopaminergic and/or cholinergic mechanisms.

Isolation induced activity deficit has been reported to be reduced with Diltiazem and Verapamil in rats<sup>10</sup>. Ethanol and Benzodiazepine withdrawal induced activity deficit was reduced following treatment with Verapamil, Diltiazem, Nicardipine<sup>11</sup> but Nitrendipine was ineffective<sup>12</sup>. These variable reports and heterogeneity of calcium channel blockers like Diltiazem a benzothiazepine, Flunarizine a piperazine and Nifedipine a dihydropyridine, both chemically and functionally prompted the present study to investigate some central nervous system activities like Isolation combativeness and suppression of conditioned avoidance response on the albino rats. The models chosen are pharmacologically validated and Benzodiazepine show a strong profile<sup>13</sup>. Hence Diazepam was used as positive control to compare the results of the test drugs.

### 1.1 Aim and objective

This study has been undertaken to evaluate possible:

- Central nervous system activities of three calcium channel blockers: Diltiazem, Nifedipine and Flunarizine.
- Comparison of their effects with established anxiolytic agent like Diazepam .

## 2. Material and Method

### 2.1 Animals

Male albino rats weighing between 250-300gms were used. Animals were divided into different groups. Each group comprised of five animals. During screening of suppression of isolation induced combativeness animals of group i, ii, iii were treated with three doses of Diltiazem viz.; 5mg/kg, 10mg/kg, 20mg/kg of body weight intraperitoneally. Animals of group iv, v, vi were treated with three different doses of Flunarizine viz; 5mg/kg, 10mg/kg, 20mg/kg of body weight intraperitoneally. Animals of group vii, viii, ix were treated with three different doses of Nifedipine viz.; 2.5mg/kg, 5mg/kg, 10mg/kg of body weight intraperitoneally. Animals of group x and xi received two different doses of Diazepam viz.; 0.25 mg/kg and 0.5mg/kg of body weight intraperitoneally. During screening of suppression of conditioned avoidance response of trained animals of group i, ii, iii were treated with three different doses of Diltiazem viz.; 5mg/kg, 10mg/kg, 20mg/kg of body weight intraperitoneally. Animals of group iv, v, vi were administered three different doses of Flunarizine viz.; 5mg/kg, 10mg/kg, 20mg/kg of body weight intraperitoneally. Animals of group viii, viii, ix were treated with three different doses of Nifedipine viz.; 2.5mg/kg, 5mg/kg, 10mg/kg of body weight intraperitoneally. Animals of group x were treated with normal saline.

### 2.2 Schedule of Drug Administration

In screening suppression of conditioned avoidance response the control group was given saline; thirty minutes prior to the test. All three drugs were given to their respective groups of animals thirty minutes before test. During screening of suppression of isolation induced combativeness; control group was given Diazepam thirty minutes before the test. Animals of test groups were given their respective drugs thirty minutes prior to the test.

### 2.3 Techniques Used

**2.3.1 Isolation induced combativeness:** Albino rat were isolated in a cage for three weeks so that no other animals can be seen<sup>14</sup>. They were not disturbed except for replacement of food. The rats became aggressive when a rat kept in group was placed with the isolated aggressive rat. Isolated rat attacked the other rat or put its nose around the anogenital region, tried to mount and climb upon the other rat. After interaction for five minutes, the second rat was removed from the cage of aggressive rat.

Isolated rat was given the test drug. After thirty minutes rat reared in group was placed in the cage with the isolated rat and was tested for aggressiveness. The isolated rat was considered tranquillized if no fighting occurred

**2.3.2 Methodology for determination of effect on behavior by classical conditioning:** In classical conditioning animals are trained to act in a certain way on a given signal to avoid a noxious stimulus or to obtain a reward.

The animals were trained to jump up the walls of the cage as soon as it receives the shock. This response is termed as 'escape response'. Once this response is established, electric shock is presided by ringing of bell.

After giving a few such shocks followed by ringing the bell, most of the animals start jumping up the walls of the cage by ringing the bell alone. This response is called as 'conditioned avoidance response'. Techno Jumping box was the instrument used for this purpose.

**Procedure:** The procedure employed is a modification of that of Cook and Weidley (1957)<sup>15</sup>, described by Sharma and Dandiya (1962)<sup>16</sup>. Rat was placed in the jumping box to reach the safer compartment. Before each experiment the rat was left undisturbed for ten minutes. After that conditioned stimulus (sound of buzzer) was given and when the rat does not

react by jumping into the other compartment of the cage, the electric shock was given. Three stimuli were given at regular intervals of one minute at a time. After one hour same procedure was repeated four times. Within five days rats were so trained that they jumped into other compartment within three second as soon as they were placed in first compartment. The time was recorded in seconds. The time required to jump from one compartment to safer compartment is known as 'reaction time'. Reaction time was obtained before drug administration and then mean was taken to give a single pre drug reaction time to reach the animal to reach safer compartment. Reaction time was measured after thirty minutes of administration of drug to the rat.

### 3. Result

The experiments were carried out with each group consisting of 5 rats and drugs were administered intraperitoneally. The results of experiments are as below:

**Table 1. Suppression of Isolation Combativeness**

Sl. No.	Drug & Dose (i.p.)	Following grouped rat	Sniffing	Side to side posturing	Climbing	Aggressive posture	Biting and fighting	Inference
1	Isolated Rat (control animal)	+	+	+	+	++	+++	Aggressive
2	Diazepam 0.25 mg/Kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
3	Diazepam 0.5 mg/Kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
4	Diltiazem 5 mg/kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
5	Diltiazem 10 mg/kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
6	Diltiazem 20 mg/kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
7	Flunarizine 5 mg/kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
8	Flunarizine 10 mg/kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
9	Flunarizine 20 mg/kg	No reaction	No reaction	No reaction	No reaction	No reaction	No reaction	Complete calming effect (+++)
10	Nifedipne 2.5 mg/kg	+	+	+	+	No reaction	No reaction	Partial calming effect (++)
11	Nifedipne 5 mg/kg	+	+	+	+	No reaction	No reaction	Partial calming effect (++)
12	Nifedipne 10 mg/kg	+	+	+	+	No reaction	No reaction	Partial calming effect (++)

**Table 2. Suppression of Conditioned Avoidance Response**

Sl. No.	Drug & Dose (i.p.)	Reaction before giving drug	Reaction without stimulus	Reaction after Buzzer	Reaction after electric shock
1	Normal Saline (Control Animal)	Jumped spontaneously	Jumped without stimulus	-	-
2	Diltiazem 5 mg/kg	Jumped spontaneously	No response	No response	No response
3	Diltiazem 10 mg/kg	Jumped spontaneously	No response	No response	No response
4	Diltiazem 20 mg/kg	Jumped spontaneously	No response	No response	No response
5	Flunarizine 5 mg/kg	Jumped spontaneously	No response	No response	Jumped
6	Flunarizine 10 mg/kg	Jumped spontaneously	No response	No response	Jumped
7	Flunarizine 20 mg/kg	Jumped spontaneously	No response	No response	Jumped
8	Nifedipne 2.5 mg/kg	Jumped spontaneously	No response	Jumped	Jumped
9	Nifedipne 5 mg/kg	Jumped spontaneously	No response	Jumped	jumped
10	Nifedipne 10 mg/kg	Jumped spontaneously	No response	Jumped	Jumped

### 4. Observations

**4.1 In case of conditioned avoidance response:** Diltiazem in all the three doses 5mg/kg, 10mg/kg, 20mg/kg; effectively calm down the animals. Effect was quite comparable to that of Diazepam used as control drug. Flunarizine and Nifedipine in a dose of 20mg/kg and 10mg/kg respectively; effectively calm down the animals. All the three calcium channel blockers seem to be most effective in combating aggressive behavior. Flunarizine and Nifedipine were effective in higher doses.

**4.2 In case of conditioned avoidance response:** In control group rats jumped spontaneously as soon as placed in jumping

cage. Diltizem when administered ; in all the three doses viz.; 5mg/kg, 10mg/kg and 20mg/kg did not jumped to safer compartment even after giving sound as well as electric shock stimulus. Flunarizine when administered; in all the three doses viz.; 5mg/kg,10mg/kg and 20mg/kg the rats jumped after giving electric shock stimulus. Nifedipine, when given in three different doses viz.; 2.5mg/kg,5mg/kg and 10mg/kg, the animals jumped to safer compartment after giving sound stimulus in all dosage.

Out of three calcium channel blockers employed in the investigation, Diltiazem seems to be most effective in blocking conditioned avoidance response whereas other two calcium channel blockers: Flunarizine and Nifedipine were only partly effective. This effect of these drugs seems to be dose dependant.

## 5. Discussion

Present study shows that calcium channel blockers suppress conditioned avoidance response. This effect was dose dependant and varied from one compound to another. The study clearly highlights that calcium channel blockers allay aggressiveness and produce a calming effect in experimental models. It is difficult to delineate the exact mechanism of central activities of calcium channel blockers. Various theories have been put forwarded to explain different mechanism of central nervous system activities of this group of drugs. The antipsychotic agents are highly effective in agitation and psychotic states including schizophrenia, hypomania and delirium. These have revolutionized the management of schizophrenia. Although it is not possible to duplicate conditions in animals for which neuroleptic drugs are used in man, a battery of animal tests may be employed to decide whether to proceed with clinical trials or not .

Shibuya *et al* (1999)<sup>17</sup> demonstrated that to develop a new concept of centrally acting drugs, the modulation of brain calcium ion flux must be considered as one of the important factors. This is because excessive calcium ion influx to neuronal cells damages or kills these cells and also because abnormal intercellular calcium ion concentrations induce several type of disorders. Recently both clinical and pre clinical studies indicate that some calcium channel blockers will be useful in the treatment of grandmal epilepsy<sup>18</sup>, manic depressive illness<sup>19</sup>, panic disorders<sup>20</sup> and anxiety<sup>21</sup>. To invoke the notion direct central action, it must be assumed that calcium channel blockers might cross the blood brain barrier. If substantiated, such direct central effect of calcium channel blockers may explain both the psychotropic effects and neuronal protection<sup>22</sup> by these agents. To investigate the actual therapeutic effect of calcium channel blockers on psychotropic disorders and neuronal death, a suitable animal model and reasonable methods and criteria must be established. Then, both preclinical and clinical studies can be expected to relate to atypical central activity of drugs modulating the brain calcium ion channels and also to the development of new pharmacological properties of calcium ion blockers.

Fulga *et al* (1991)<sup>23</sup> studied the anxiolytic effect of the calcium channel blockers like Nifedipine and Verapamil. Data were considered important for a new future aboard of the treatment and pathophysiology of the anxiety. Gopal *et al* (2001)<sup>15</sup> studied that the possible mechanism involved in the behavioral disinhibitory effects of calcium channel blockers could be not only due to their primary action, inhibition of calcium ion influx, but has also due to intersection with serotonergic receptors<sup>24</sup>, dopaminergic receptors<sup>25</sup>, increased adenosine concentration at synaptic sites<sup>26</sup>, decreased release of corticotrophin releasing factors<sup>27</sup> and sodium channel blockade etc. Since the anxiolytic profile differs amongst individual calcium channel blockers a detailed study to define their precise mechanism is needed.

Green *et al* (1990)<sup>25</sup> studied the effect of calcium blockers on behavior mediated by 5-HT in rats and mice together with an investigation on the effect of these drugs on 5-HT synthesis in rat brain and endogenous 5-HT release from brain slices. Data indicate that at a high dose, calcium ion blockers produce complex changes in 5-HT function in rodents which are similar to those produced by lithium administration.

Boullin *et al* (1987)<sup>25</sup> suggested that calcium channel blockers have action on serotonergic mechanisms : Uhr *et al* (1986)<sup>28</sup> reported reduced platelet 5-HT in normal and schizophrenic subjects given Verapamil. Calcium channel blockers have been reported to inhibit platelet 5-HT uptake and Imipramine binding in brain and platelet<sup>29</sup>; to have synergistic effects when given in combination with Lithium<sup>30</sup> and Carbamazepine<sup>31</sup>. Diltiazem may be effective in tardive dyskinesia.

Srivastava *et al* (1989)<sup>32</sup> studied that calcium channel blockers affect release of central neurotransmitters including noradrenaline and 5-HT, which are involved in depression, the behavioral despair test was used to investigate the effect of calcium channel blockers on depression. Verapamil and Diltiazem produced a dose dependant increase in immobility time, indicating facilitation of depression, while Nifedipine significantly reduced the immobility time, indicating an antidepressant activity. Verapamil and Diltiazem blocked the antidepressant effect of Desipramine, Clomipramine, Mianserine and Tranylcypromine; indicating the involvement of various mechanisms in the facilitating effect of Verapamil and Diltiazem on depression. The antidepressant effect of Nifedipine may be attributed to the blockade of presynaptic alpha-2 receptors. The antagonism exhibited by calcium channel blockers suggest that behavioral sensitization involves calcium ion and L-type calcium channel.

Pucilowski *et al* (1989)<sup>33</sup> studied that the significant progress in the field has been made possible with the

broadening use of organic calcium channel blockers. Until recently considered, almost exclusively as peripherally active, antianginal and antiarrhythmic drugs. Calcium channel blockers however do penetrate the blood brain barrier from the periphery. The existing evidence suggest that calcium channel blockers have marked psychotropic properties. The profile of their central activity is unique and spans a wide range of effects. Antkiewicz *et al* (1999)<sup>34</sup> studied that ion channels can be divided into two main groups, receptor operated channel and voltage operated channels. In number of neurons various subtypes of calcium ion channels occur together. Among them the L-type calcium ion channel has been described first and most studied. The L-type calcium channel is localized on nerve terminals in the pre and post synaptic parts as well as on cell bodies and may be involved in the mechanism of psychotropic drugs. Chronic treatment with various psychotropic drugs, changes the density of L-type calcium ion channels in the central nervous system. L-type voltage operated channel is involved in responsiveness to pain, morphine tolerance and dependence and adaptation changes induced by several chronic treatment with psychotropic drugs. Thus according to pharmacological and also clinical data, L-type calcium ion channels may be involved in etiology of variety of psychotropic disorders, Soubrie *et al* (1990)<sup>35</sup> reviewed the preclinical evidence suggesting that calcium channel blockers exert bio-behavioral effects that may have some relevance central nervous system pharmacology and thus to psychiatry. This survey suggest that calcium channel blockers especially dihydropyridine derivatives share all these profiles together. There are however important limitations in the interpretation of pre clinical data where the various calcium channel blockers may have different profiles and thus varying potential psychiatric applications, cannot be explored in depth as there are few comparative data on these drugs on a large variety of animal models. In addition, the doses of calcium channel blockers reported to produce behavioral response are generally higher than the dose sufficient to produce other pharmacodynamic actions. Thus possibility that these former responses could be secondary to these later actions cannot be excluded.

## 6. Summary and Conclusion

From present study it can be concluded that calcium channel blockers in different dosage can effect central nervous system in different ways and can interact with some other drugs effective on central nervous system. This may be due to blockade of neuronal and long lasting current type voltage sensitive calcium channels by calcium channel blockers under investigation. In addition to this mechanism, central effects of calcium channel blockers may be due to their interactions with serotonergic receptors, dopaminergic receptors, increased adenosine concentration at synaptic sites, decreased release of corticotrophin releasing factors and sodium channel blockade etc.

This shows the potentials to find out, if a patient on Diltiazem, Flunarizine and Nifedipine therapy should be given lower doses of anxiolytics, neuroleptics and hypnotics, as their full doses may lead to their toxicity in such patients. The above findings could be potentially useful in reducing the doses of anxiolytics, neuroleptics. There are however important limitations in the interpretation of pre clinical data where the various calcium channel blockers may have different profiles and thus varying potential psychiatric applications, cannot be explored in depth as there are few comparative data on these drugs on a large variety of animal models. In addition, the doses of calcium channel blockers reported to produce behavioural response are generally higher than the dose sufficient to produce other pharmacodynamic actions. Thus possibility that these former responses could be secondary to these later actions cannot be excluded.

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