Research article

Captopril is more effective than Perindopril against aluminium chloride induced amyloidogenesis and AD like pathology

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GRAPHICAL ABSTRACT
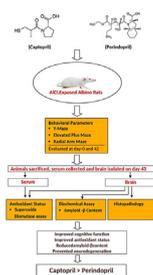
ABSTRACT

Alzheimer's disease (AD) is a common neurodegenerative disorder. Aluminium chloride induces AD like pathology in rats. Renin angiotensin system plays a significant role in the pathogenesis and occurrence of Alzheimer's disease. In the present study we evaluated and compared the effect of Captopril and Perindopril against aluminium chloride induced amyloidogenesis and cognitive dysfunction in rats. Wistar rats of both sex were divided randomly into four groups i.e. Group I was served as normal control and treated with normal saline, Group II was administered with $AlCl_3$ (100 mg/kg, p. o.) and Group III and IV received Captopril (30 mg/kg, p. o.) and Perindopril (5 mg/kg, p. o.) respectively 1hr prior to administration of $AlCl_3$. All the doses were given once daily for 42 days. The evaluation of memory function was carried out in Y-maze (spontaneous alternation), radial arm maze (number of correct responses) and elevated plus maze (transfer latency). After behavioral studies, estimation of antioxidant status (brain and serum), amyloid-β content (brain) and histopathology of brain hippocampus region was done. Administration of $AlCl_3$ for 42 days impaired cognitive dysfunction. Captopril and Perindopril prevented $AlCl_3$ induced cognitive dysfunction by improving spontaneous alternation behavior, number of correct responses and reducing transfer latency. They also increase the antioxidant status, reduce the Aβ42 content in the brain and reverse the histopathological changes caused by $AlCl_3$ in hippocampal region. Both Captopril and Perindopril protects against aluminium chloride induced amyloidogenesis and AD like pathology. Captopril is found to be more effective than Perindopril.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder associated with deficit learning and memory [1, 2]. Accumulation of extracellular senile plaques of aggregated amyloid-beta (Aβ) and the development of neurofibrillary tangles of deposited hyperphosphorylated tau proteins obstruct the communications between neuronal cells and cause cognitive dysfunction [3, 4]. It was also reported that increased concentration of reactive oxygen species (ROS) and their by-products enhance the AD onset and progression [5, 6]. Aluminium chloride induces AD like pathology in rats [4].

Renin Angiotensin System (RAS), a commonly known hormonal system, is mainly responsible to control the normal blood pressure and fluid retention system in humans. However, apart from this it also plays an important key role in central nervous system (CNS) and is responsible for generating different neurodegenerative disorders [7, 8]. Many preclinical and clinical studies confirm that RAS is responsible for the impairment of memory function. Moreover, ACE and other components of RAS are widely found in the brain and elevated levels of ACE progresses onset of AD [9].

ACEIs are basically classified into CACE-Is (centrally acting ACEIs) and non CACE-Is (non-centrally acting ACEIs). CACE-Is like Captopril, Perindopril and Ramipril possess significant ability to cross blood brain barrier (BBB) whereas non CACE-Is such as Lisinopril, Enalapril and Imidapril have poorer BBB permeability [10]. The current study is undertaken to evaluate and compare the effects of Captopril and Perindopril against aluminium chloride induced amyloidogenesis and cognitive dysfunction.

2. Material and methods

2.1. Experimental animals

Wistar albino rats of both sexes (120–200 g) were taken from the central animal house of School of Pharmaceutical Sciences, Siksha'O'Anusandhan University, Bhubaneswar. All the animals were kept under standard environmental conditions like 25 ± 3 °C temperature, 45–50% relative humidity and 12 hr light and dark cycle before the initiation of the experiment. Free food and water were accessed *ad libitum*. All the protocols used in the experiment were approved by Institutional Animal Ethical Committee of School of Pharmaceutical Sciences (IAEC/SPS/SOA/13/2020) and ethical guidelines were strictly followed during the experiments. These animals were acclimatized for 48 hours to adopt the new environment before the experimental work.

2.2. Drugs and chemicals

Captopril and Perindopril were received as gift samples from Lupin Limited (Tarapur, India). All the chemicals used for experimental purpose are of laboratory grade.

2.3. Experimental design

All the animals were selected randomly and divided into four groups consisting of six animals in each. Group-I served as Control and received saline (10 ml/kg), Group II received AlCl$_3$ (100 mg/kg, p. o.), Group III and IV received Captopril (30 mg/kg p. o.) and Perindopril (5 mg/kg, p. o.) respectively 1hr before the administration of AlCl$_3$. All the doses were administered once daily for 42 days continuously. Behavioral tests were conducted on day 0 and day 42.

On day 43, after depriving food for 12 hours, all the animals were sacrificed under human condition for the collection of serum samples and brain homogenates for the estimation of biochemical and histological studies.

2.4. Behavioral study Y-maze

Y-maze (INCO) was used for the evaluation of spatial working memory in rats. Spontaneous alternation percentage (SAP) was calculated. Y-maze consists of three equal arms at equivalent angles and named as A, B, C (length 35 cm, breadth 12 cm and height 25 cm). It also contains a triangular symmetrical central zone. The animals were placed at the edge of one arm and then they were permitted to freely walk between the arms for 8 minutes. A corrected arm entry was counted when the rat completely placed all its four limbs within the arm. Arms were wiped with alcohol free disinfectant well before each trial of the rat to get rid of any remaining odour. A repeated entrance on overlapping triplet combination pattern (ABC, BAC, CAB etc) into the three arms was known as alternation of the arm. Both total arm entries and number of alternations (3 out of 3, degree of freedom = 2) were recorded to calculate the SAP by using following equation (1) on day 0 and day 42 [11].

$$SAP = [(Number\ of\ alternations)\ /\ (total\ armentries-2)]\ *100 \qquad (1)$$

2.5. Radial arm maze

Radial arm maze (INCO) was used to study the number of correct responses in rats. Radial maze consists of 8 arms of 60 cm length each radiating from a central platform of diameter about 20 cm. Each rat was placed at the center of the maze and endorsed freely to explore the arms for 10 minutes. Entry into the arm which a rat had not visited formerly is called as correct response whereas re-entry to the same arm was considered as error. The number of correct responses by each rat before encountering the first error was noted on day 0 and day 42 [12].

2.6. Elevated plus maze

Memory was evaluated by elevated plus maze (EPM) apparatus. The maze consists of two closed arms (50×10 cm) with two opposite open arms (50×10 cm) which is plus-shaped and remain elevated above the floor level. Before experiment each rat was trained by placing them at the end of an open arm and by using a stopwatch. Transfer latency time (s), can be defined as the time taken by a rat to enter (with all four paws) into either of the closed arms. The transfer latency was observed and noted. The maze was cleaned with 70% ethanol between runs. The time taken by each animal to enter into the closed arm with all its four limbs when positioned at the edge of one open arm facing away from central platform was recorded as the initial transfer latency. A 60 sec time period cut off was set. The rat was then allowed to move freely inside the maze regardless of open and closed arms for another 10 sec. After 24 hours the retention transfer latency test was performed in the same way as in the acquisition trial. If the rat did not enter the enclosed arm within 60 sec on 2nd trial, the transfer latency (day 0) was assigned 60 sec [11]. The rats were again put into the elevated plus maze on day 42 to evaluate the transfer latency.

2.7. Sample preparation

After completion of all behavioral models, rats from each group were decapitated under anesthesia with ketamine (87.5 mg/kg)/ xylazine (12.5 mg/kg) cocktail. Then the serum samples were collected for estimation of superoxide dismutase (SOD) content. The brain tissues (n = 3) were immediately removed and cleaned with cold saline over the ice and used for brain homogenate preparation (n = 3) and the rest were stored in 10% formalin solution for histopathology studies (n = 3).

For antioxidant assay and estimation of Aβ content, the brain homogenates were prepared. The brain tissues (n = 3) were homogenized with 0.3 M of phosphate buffer (pH 7.4) at a ratio of 1:3 using a homogenizer at oscillation frequency of 180–1800 per minute. The homogenates were then centrifuged for 15–20 minutes at 4 °C approximately at 15000 rpm by a cooling centrifuge and finally the obtained supernatant was collected and stored at-80 °C till the assay to be performed.

2.8. Antioxidant (SOD) assay

The superoxide dismutase (SOD) assay was performed by UV-visible (JASCO-630) spectrophotometer. A blank solution was prepared by adding 1 mM of EDTA (0.5 ml), 0.05 mM of Tris buffer (1.5 ml) and 0.2 mM of Pyrogallol (1 ml) and considered as control. The test preparation consisted of blank solution added with 50 μl of brain homogenate or plasma in a separate test tube. The change in the absorbance was observed and recorded against the control at 420 nm. Then the % of protection was calculated using following equation (2).

$$\%\text{Protection} = (A_{control} - A_{test})/ A_{control} \times 100 \qquad (2)$$

The SOD content was obtained by putting each percentage of protection in standard curve (Y = 56.53x-0.1198, R^2 = 0.99) and expressed as mmol/L [12, 13].

2.9. Detection of amyloid-β content

A sandwich ELISA kit (Elab science) was used for the evaluation of amyloid-β content in the brain. For the estimation of Aβ, the standard solution was prepared using serial dilution method to obtain a standard calibration curve. Then the protein concentration was assayed by BCA (bicinchoninicacid) assay method. About 100 μl containing 250 μg of protein from soluble fraction of $A\beta_{1-42}$ was incubated in the micro-plate pre-coated with their corresponding antibodies; sample solution was added and incubated for 90 minutes at 37 °C. Then the micro-plate well was washed with 350μl of wash buffer solution and incubated with 100 μl of biotinylated detection antibody for 60 minutes at 37 °C. After incubation samples were washed and HRP-labeled conjugate was added to each well and incubated for 30 minutes, washed again and incubated with a substrate reagent of 50μl for 15 minutes at 37 °C and finally 40 μl of stop solution was added to stop the reaction. Then it was preheated for sometime at same temperature and optical density was measured by ELISA reader at a wavelength of 450 nm [14].

2.10. Histopathology

The brain tissues (n = 3) were fixed and dehydrated in different solutions of ethanol and water followed by cleaning with xylene. Then the cleaned tissues were embedded in paraffin and sections of 5–6 μm thickness were prepared. Finally the tissues were stained with haematoxylin and eosin dyes and mounted on the trinocular biological

microscope (LYNX) at 450x magnification for clear observations of brain images of different group of animals [12].

2.11. Statistical analysis

The experimental data were expressed as mean ± SD. The statistical analysis was done using one-way ANOVA followed by Tukey post hoc t-test using SPSS version 20.0. $p < 0.05$ was considered as the level of significance.

3. Results

3.1. Pharmacological screening models Y-Maze

Group II animals administered with $AlCl_3$ exhibit cognitive deficit which significantly ($p < 0.05$) decreases the spontaneous alternation percentage as compared to normal control. The effect of $AlCl_3$ was significantly reduced by Captopril and Perindopril. However, Captopril showed more significant ($p < 0.05$) effect than Perindopril (Table 1).

3.2. Radial arm maze

In radial arm maze test, the number of correct responses was significantly ($p < 0.05$) reduced by administration of $AlCl_3$ continuously for 42 days as compared to normal control group. Treatment with Captopril or Perindopril significantly ($p < 0.05$) improved the number of correct responses as compared to $AlCl_3$ treated groups. Captopril was more effective ($p < 0.05$) than Perindopril (Table 2).

3.3. Elevated plus maze

In elevated plus maze, treatment of $AlCl_3$ significantly increased ($p < 0.05$) the transfer latency as compared to control group. Captopril and Perindopril significantly ($p < 0.05$) decreased the Elevated transfer latency. However, Captopril was more effective ($p < 0.05$) than Perindopril (Table 3).

3.4. Estimation of antioxidant status

3.4.1. Estimation of superoxide dismutase

There was significant ($p < 0.05$) reduction in the superoxide dismutase content in $AlCl_3$ treated animals as compared to control animals. Captopril and Perindopril significantly ($p < 0.05$) elevated the SOD levels and reversed the effect of $AlCl_3$. Captopril exhibited more significant ($p < 0.05$) effect than Perindopril (Table 4).

Table 1. Effect of Captopril and Perindopril on spontaneous alternation behavior in Y-Maze using AlCl3 induced AD like behavior model.
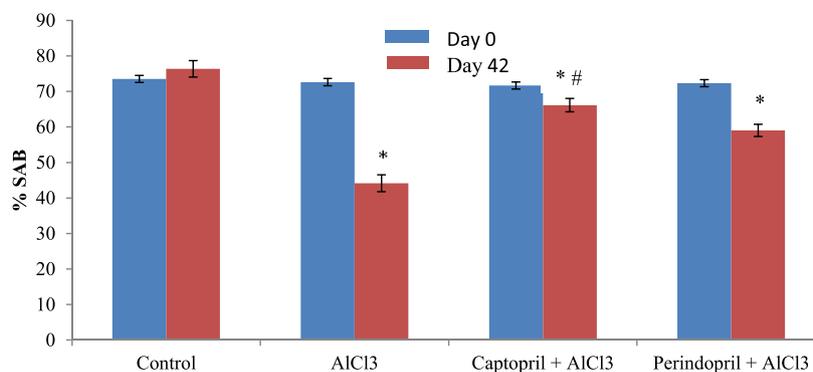
Values are expressed as Mean ± SD (n = 6) using one-way ANOVA followed by Tukey post hoc t-test.
*p < 0.05 for Gr-I Vs Gr-II, Gr-II Vs Gr-III/IV and #p < 0.05 for Gr-III Vs Gr-IV.

Table 2. Effect of Captopril and Perindopril on number of correct responses in Radial arm maze using $AlCl_3$ induced AD like behavior model.
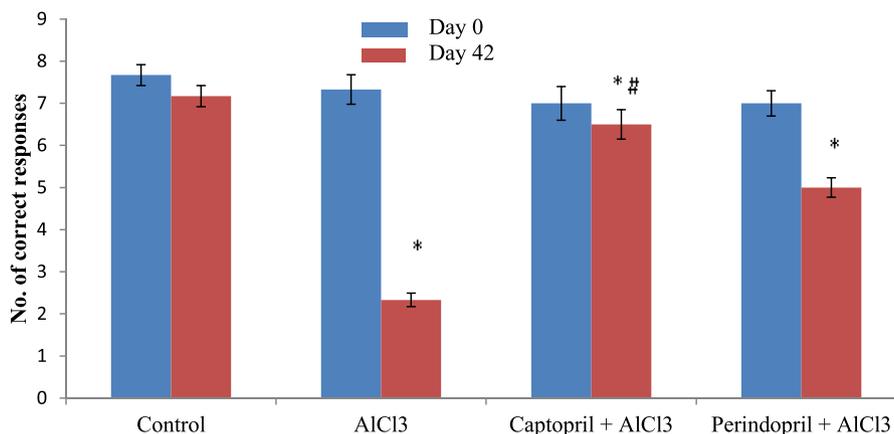
Values are expressed as Mean $\pm$ SD (n = 6) using one-way ANOVA followed by Tukey post hoc t-test.*$p < 0.05$ for Gr-I Vs Gr-II, Gr-II Vs Gr-III/IV and $^{\#}p < 0.05$ for Gr-III Vs Gr-IV.

3.4.2. Estimation of $A\beta_{1-42}$ content

The level of $A\beta_{1-42}$ in the brain of $AlCl_3$ administered rats was significantly ($p < 0.05$) increased as compared to control group of animals. The elevated $A\beta_{1-42}$ was significantly ($p < 0.05$) reduced by both Captopril and Perindopril. Captopril showed more significant ($p < 0.05$) protection than Perindopril (Table 5).

3.5. Histopathology study

Histological evaluation further confirmed the neuroprotective effect of ACE inhibitors. Control group showed normal architecture with organized neuronal glial cells whereas $AlCl_3$ administered animals produced neurodegeneration and hemorrhages which is evident with marked loss of normal neuronal cells and their nuclei. This effect was prevented by ACEIs (Captopril and Perindopril) indicating their neuroprotective action against $AlCl_3$ (see Figure 1).

4. Discussion

Alzheimer's disease is the common cause of dementia in elderly people which generally accounts 60–70% of cases. AD and all other types of dementia are estimated to increase to approximately about 65 million by 2030 [15]. Metal ion haemostasis in the brain plays an important role in normal functioning of the cells and neurons [16] and their deregulation leads to neurodegeneration progression. There are several metals such as aluminium, iron, zinc, copper, silica, lead, lithium and mercury which are responsible to produce neurotoxicity [17].

Aluminium is a ubiquitous metal which can cause neurodegenerative disorder and cognitive deficit by enhancing oxidative stress, decreasing cholinergic neurotransmission and causing neuronal inflammation [18, 19, 20]. Aluminium mainly crosses blood brain barrier (BBB) and gets deposited in the cortex, hippocampus and cerebellum region of the brain to induce AD like pathology [21]. The present study also agrees with

Table 3. Effect of Captopril and Perindopril on transfer latency in elevated plus maze using $AlCl_3$ induced AD like behavior model.
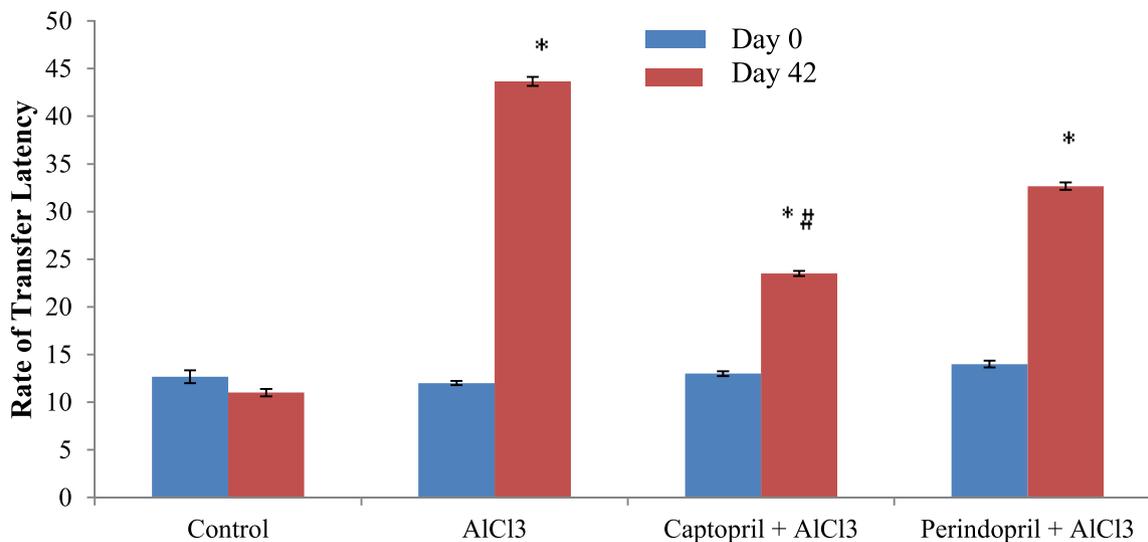
Values are expressed as Mean $\pm$ SD (n = 6) using one-way ANOVA followed by Tukey post hoc t-test. *$p < 0.05$ for Gr-I Vs Gr-II, Gr-II Vs Gr-III/IV and $^{\#}p < 0.05$ for Gr-III Vs Gr-IV.

Table 4. Effect of Captopril and Perindopril on superoxide dismutase (SOD) content in rat brain and serum using AlCl$_3$ induced AD like behavior model.
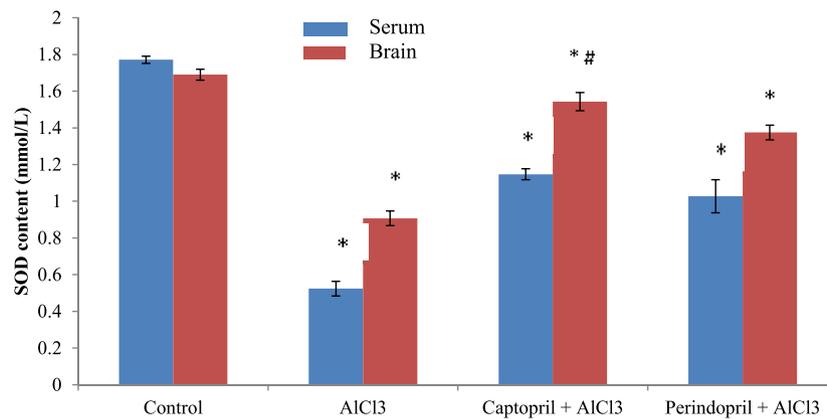
Values are expressed as Mean $\pm$ SD (n = 6). One-way ANOVA followed by Tukey post hoc t-test. *$p <$ 0.05 for Gr-I Vs Gr-II, Gr-II Vs Gr-III/IV and #$p <$ 0.05 for Gr-III Vs Gr-IV.

Table 5. Effect of Captopril and Perindopril on Aβ_{1-42} content in rat brain using AlCl$_3$ induced AD like behavior model.
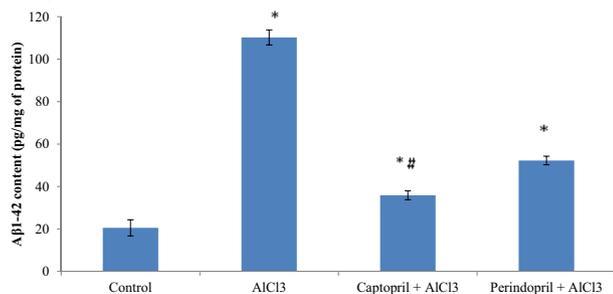
Values are expressed as Mean $\pm$ SD (n = 6) using one-way ANOVA followed by Tukey post hoc t-test. *$p <$ 0.05 for Gr-I Vs Gr-II, Gr-II Vs Gr-III/IV and #$p <$ 0.05 for Gr-III Vs Gr-IV.

these findings as chronic administration of AlCl$_3$ impairs the spatial learning and memory function in rats by promoting amyloidogenesis and oxidative stress.

In RAS pathway, the angiotensinogen is mainly converted to Ang-I (angiotensin-I) in the presence of renin. Afterwards, Ang-I is converted to Ang-II (angiotensin-II) via ACE (angiotensin converting enzyme) [22]. Recent experimental and clinical research have reported that RAS plays a significant role in pathophysiology of AD development [23, 24, 25, 26]. Moreover, several experimental findings also indicate that the activation of RAS causes neuronal damage followed by neurodegenerative disorders while, blockade of RAS attenuates the neurodegeneration [9, 27]. It was also reported that the involvement of excessive ACE/Ang II (angiotensin II) in brain induces oxidative stress, neuro inflammation and cell apoptosis causing several brain disorders [28]. Several studies reported that Ang-II is responsible for the cognitive dysfunction as it accumulates amyloid-β, aggregates tau proteins, inflicts oxidative stress, produces neuroinflammation and is responsible of neurotransmitter aberrations [29].

Captopril and Perindopril, being ACE inhibitors, decrease the level of Angiotensin II. Again both these drugs can cross the BBB [10]. Captopril significantly deteriorates the ischaemia induced brain damage [30]. Captopril is also a potent anti-inflammatory agent and ameliorates Aβ production, enhances microglial activation and phagocytosis there by improving cognitive dysfunction [31]. Perindopril also exhibits inhibitory effect on lipopolysaccharide induced amyloidogenesis and cognitive dysfunction in mice model [32, 33]. So the present study is undertaken to compare the efficacy of captopril and perindopril against AlCl$_3$ induced amyloidogenesis and AD like pathology.
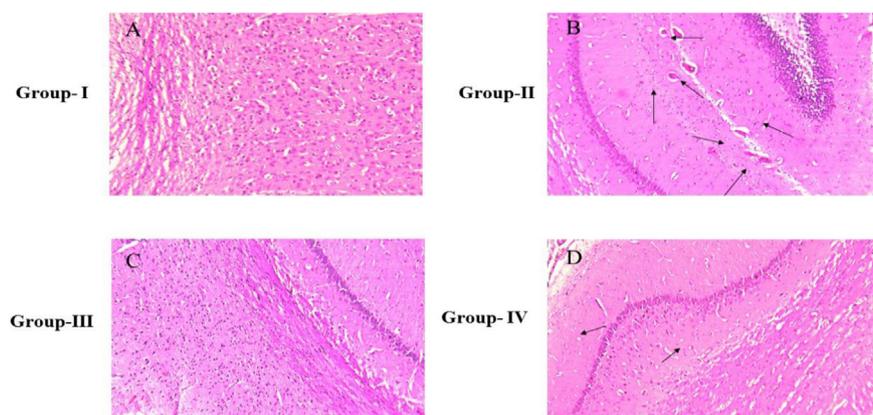
Figure 1. Histology of hippocampal region of brain A (control): It shows normal and organized neuronal cells. B (AlCl$_3$): It shows neurodegeneration as there is presence of pyknotic nuclei, dead neuronal structure and focal hemorrhages. C (Captopril): It significantly reduces the neurodegeneration with appearance of normal cyto-architecture of neuronal glial cells. D (Perindopril): It shows reduced neurodegeneration.

Behavioral models such as elevated plus maze, Y-maze and radial arm maze are generally used for evaluating the memory and cognitive functions in the rodents [11, 12]. Our results demonstrated that $AlCl_3$ significantly ($p < 0.05$) reduced spontaneous alternation behavior (Y-maze), number of correct responses (radial arm maze) and significantly increased transfer latency (elevated plus maze). Captopril and Perindopril significantly ($p < 0.05$) improved spontaneous alternation behaviour, number of correct responses and significantly reduced transfer latency in $AlCl_3$ treated rats. This is in agreement with earlier reports of efficacy of Captopril and Perindopril against other models of cognitive dysfunction. Captopril is found to be more effective ($p < 0.05$) than Perindopril.

The amyloid-β aggregation is represented as the major hallmark for the AD pathogenesis and in this present effort significant ($p < 0.05$) elevation of $A\beta_{1-42}$ protein was observed in hippocampus of $AlCl_3$ administered animals. This is in agreement with earlier findings [34]. Perindopril facilitates its entry to BBB and significantly attenuates Aβ aggregation, hyperphosphorylated tau protein levels, oxido-nitrosative stress and apoptotic markers [35]. Captopril also retards the development of neurodegeneration by decreasing the amyloidogenesis of amyloid precursor proteins, enhanced reactive oxygen species (ROS) and decreased α and γ-secretase levels [30]. Our results revealed that Captopril and Perindopril significantly reduced the $AlCl_3$ induced elevated Aβ42 in rats. This further validates the efficacy of Captopril and Perindopril in AD.

Due to high oxygen depletion, presence of more polyunsaturated fatty acids and feeble antioxidant defense system the hippocampus is readily susceptible to oxidative imbalance [36, 37]. The resulting oxidative stress and oxidative imbalance initiates impairment to the bio molecules and increasing evidence suggests that oxidative stress plays a crucial role in AD [6, 38]. Moreover, elevation in nitric oxide (NO) levels in AD brain induces nitrosative damage and further this NO combines with ROS to produce a highly toxic compound i.e., peroxynitrite ($ONOO^-$) which results in cell apoptosis [38, 39]. Chronic administration of aluminium develops oxidative stress [40, 41]. In our study, $AlCl_3$ significantly ($p < 0.05$) reduced the SOD content thereby causing oxidative stress.

Oxidative stress plays an important role in progression and development of AD by aggravating Aβ and tau protein formation, mitochondrial dysfunction and energy failure and by reducing the levels of antioxidant enzyme (eg:superoxide dismutase, catalase) [42]. $AlCl_3$ significantly increases oxidative stress which induces Aβ production and accumulates in the transgenic mice hippocampus leading to AD [34]. ACE inhibitor (Captopril) and angiotensin receptor blocker (Valsartan) significantly improve cognitive function in streptozotocin induced dementia in rats by potentiating the antioxidant status of brain defence system [43]. Our study also revealed that Captopril and Perindopril produce significant ($p < 0.05$) elevation in the antioxidant status by increasing the SOD content in $AlCl_3$ treated rats.

In the histopathology study, control animals show normal organization and architecture of neuronal cells with nuclei in rat brain. $AlCl_3$ produces marked neurodegeneration of neuronal cells due to presence of pyknotic cells, hemorrhages and dead neuronal cells. This neurodegeneration was less in Captopril and Perindopril treated rats. Captopril shows better and organized neuronal glial cells in comparison to Perindopril.

5. Conclusion

Captopril and Perindopril easily cross BBB and improve cognitive functions by reversing $AlCl_3$ induced reduced spontaneous alternation behavior (Y-maze), reduced number of correct responses (radial arm maze) and increased transfer latency (elevated plus maze). Increase in the antioxidant status and reduction in the Aβ formation may be attributed to their efficacy against cognitive dysfunction. This is also supported by the histological studies. Captopril is found to be more effective than Perindopril against $AlCl_3$ induced AD like pathology in rats.

Declarations

Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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