

Original Article

Targeting of adenylate cyclase and protein kinase A: An advanced concept of Alzheimer's disease pharmacotherapy

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ABSTRACT

Objectives: The extremely low efficiency of existing methods of treating Alzheimer's disease (AD) makes it highly relevant to develop fundamentally new drugs for its therapy. It is advisable to create drugs that stimulate neurodegeneration. As part of the implementation of this route, it is promising for the identification of targets from numerous intracellular signalling molecules, including Cyclic adenosine monophosphate (cAMP)-dependent intracellular pathways. The work objective was to explore the potential of regulating the brain regeneration-competent cells (progenitors and neurogliaocytes of various types) using the adenylate cyclase and protein kinase A blockers under conditions of the neurotoxic effects of beta-amyloid *in vitro*.

Materials and Methods: The C57BL/6 mice were used. The functioning of neural stem cells (NSCs), neuronal committed progenitor (NCP) cells and neurogliaocytes of the subventricular zone of the brain under the influence of blockers of adenylate cyclase (Chemical Abstracts Service [CAS] number 6698-26-6) and protein kinase A (CAS 108068-98-0) was studied. NCP, astrocytes, oligodendrocytes and microgliaocytes were obtained from neural tissue using immunomagnetic sorting.

Results: We revealed the discoordination of the activity of NSC and NCP under the action of neurotoxic β -amyloid. The ability of the adenylate cyclase and protein kinase A blockers to synchronise the implementation of the progenitors' functions when exposed to beta-amyloid was found. The blockade of cAMP-dependent pathways on exposure to a neurotoxic agent also enhanced the secretion of stimulatory neural progenitors by several types of neurogliaocytes. Particularly pronounced was the reaction of oligodendrocytes and microglial cells during protein kinase A inactivation.

Conclusion: The results show the potential of coordinated stimulation of the functions of different progenitors and neurogliaocytes using selective inhibitors of intracellular molecules of cAMP-dependent pathways (primarily protein kinase A) in Alzheimer's dementia.

Keywords: Adenylate cyclase, Alzheimer's dementia, Neurogenesis, Protein kinase A, Regeneration-competent cells

INTRODUCTION

The spread of Alzheimer's disease (AD) is now reaching epidemic levels, and (for unknown reasons) to a greater extent in economically more developed countries.^[1] At the same time, the onset of the disease occurs at an increasingly earlier age, and the rate of progression of its pathological manifestations steadily increases. To treat it today, medicines that affect neurons

are used. However, they are not effective and cannot stop the process of neurodegeneration.^[2,3] AD aetiology is not completely clear,^[1,4,5] but many parts of its pathogenesis are known. In particular, the role of pathogenic beta-amyloid fragments in damaging nerve cells is well known.^[5-7] It was found that dysfunction of neurons, their necrosis and apoptosis under conditions of exposure to amyloid aggregates occur with the loss of neuroplasticity and neurogenesis.^[5,8,9]

Our previous studies have shown that neurogenesis disorders in AD develop against the background of uncoupling of the mitotic ability and specialisation processes of neural stem cells (NSCs) and the neuroglial neurotrophin-secreting function.^[10,11]

Based on this, the development of anti-AD drugs that coordinate the activity of cells involved in brain regeneration (NSC, neuronal committed progenitor (NCP) cells and neuroglial cells) looks promising.^[5,10] The development of this direction seems preferable through the concept of control of intracellular signalling in cells involved in regeneration (CIR).^[3,12-15] The effectiveness of selective action is determined by the specificity of signal transmission in the precursors of different tissues and/or the presence of unique isoforms in them.^[3,16] The most important stages in the development of this concept of AD treatment are the identification of specific signalling molecules that can radically influence the activity of RCC. The most important stage in the development of this strategy is the pinpointing of specific 'targets' that can radically influence the activity of CIR.

It is well known that cAMP largely controls the functions of NSCs and neuroglial cells, including in some types of nervous tissue degeneration.^[12,17-19] However, the significance of individual protein-protein interactions within this signalling for the functioning of NSC and a number of other neural CIR involved in neuroregeneration in AD is still unknown.

The work objective was to explore the potential of regulating the CIR brain (NSC, NCP, astrocytes, oligodendrocytes and microglial cells) functions using the adenylate cyclase and protein kinase A blockers during the neurotoxic effects of beta-amyloid.

MATERIALS AND METHODS

Chemicals

Beta-amyloid 25–35 (Sigma-Aldrich, Germany); adenylate cyclase blocker (CAS 6698-26-6, Sigma-Aldrich, USA); protein kinase A blocker (CAS 108068-98-0, Sigma-Aldrich, USA); special MACSNeuroMedium; MicroBeads for immunomagnetic sorting (antibodies to polysialylated-neural cell adhesion molecule [PSA-NCAM]; antibodies to astrocyte cell surface antigen-2 [ACSA-2]; antibodies to

Anti-O4; antibodies to CD11b) (Miltenyi Biotec B.V. and Co. KG, Germany); hydroxycarbamide, hydurea and dimethyl sulfoxide solution (Sigma-Aldrich, USA).

Experimental animals and study design

During the work, we were guided by the principles of humane treatment of animals. Permission was given by the Special Ethical Committee of the Tomsk National Research Medical Centre (details of protocol: GRIPhRM-2023-01/11 dated 12 January 2023). The carbon dioxide (CO₂) chamber was used to kill the mice after completion of the work.

In vitro detected the influence of the adenylate cyclase (30 μM) and protein kinase A blockers (10 μM) on the NSC, NCP and the neurotrophin (humoral factors stimulating neural progenitors) secretion by astrocytes, oligodendrocytes and microglial cells under conditions of the neurotoxic effects of beta-amyloid.^[5,10] The cell cultures without beta-amyloid and with this poison without inhibitors served as controls.

Neurotoxic effects of beta-amyloid modelling

The neurotoxic effects of beta-amyloid were modelled by introducing the βA 25–35 fragment *in vitro*. This poison (1 mM) was first kept in saline for 7 days for protein aggregation. When culturing cells, the concentration of βA *in vitro* was 20 μM.^[5,10]

Progenitors research

Tissue was isolated from the subventricular zone to obtain progenitors. The NSC and NCP in the cellular material were calculated by the level of colony formation in cultures of unfractionated and CD56⁺(PSA-NCAM⁺)-expressing cells, respectively. CD56⁺ cells were isolated by immunosorting using PSA-NCAM MicroBead.^[10,15,16] After this, the progenitors were 5 days incubated in MACS Neuro Medium (10⁵/mL) in the CO₂ incubator under standard conditions (37°C, 5% CO₂). NSC and NCP in the studied cellular material were assessed by colony-forming capacity (by the number of CFU consisting of at least 100 cells). The progenitor mitotic capacity was also determined. For this purpose, we used hydroxyurea (1 μM), which blocks the mitosis S-phase. In addition, the ratio of the number of cluster-forming units (by the number of cluster-forming units consisting of 30–80 cells) to CFU was determined by the NSC and NCP specialisation index (specialisation index).^[5,15]

Neuroglial cells research

The astrocytes, oligodendrocytes and microglial cells were obtained using microbeads with antibodies to ACSA-2, Anti-O4 and CD11b, respectively. The supernatants of

these neuroglial cells ($10^5/\text{mL}$) were then obtained (2 days incubated under standard conditions). Based on the level of yield of spherical cell formations colony-forming units (CFU) under the influence of the resulting conditioned media, the activity stimulating neurosphere formation (neurosphere stimulating activity [NSA], the content of a complex of humoral factors stimulating neural progenitors) was determined.^[5,14]

Statistical analysis

For data analysis, the Mann–Whitney test was used. The results in the article are presented as arithmetic means, and the significance level of differences is noted at $P < 0.05$.^[20]

RESULTS

NSC and Neuronal committed progenitors (NCP) when exposed to beta-amyloid

The toxic effect of βA 25–35 on precursors was manifested in a decrease in the yield of NSC_CFU (up to 78.1% of the intact control level) and their mitotic activity [Figure 1a-c]. There was also an increase in the number of NSC_CIFU in culture with beta-amyloid (up to 138.7% of the same indicator in a medium without beta-amyloid) and the ratio of NSC_CIFU to NSC_CFU (up to 180.2%), reflecting the rate of NSC specialisation [Figure 1b]. The beta-amyloid, at the same time, stimulated the NCP mitotic activity. The yield of NCP_CFU [Figure 2a] and their proliferation reached 351.3% and 207.9% of control values [Figure 2a-c]. At the same time, the rate of development and maturation of multipotent precursors increased (up to 187.6% of the initial level), while in unipotent precursors, it decreased significantly (to 53.3% of the control) [Figure 2d]. These findings confirmed the data on the uncoupling of NSC and NCP activities when exposed to beta-amyloid.^[8,21] In addition, maladaptation of the cellular renewal system (in addition to shifts in the proliferation of precursors and decreased differentiation of NSCs) should be considered the rapid maturation of NSCs as a cause of aberrant cell development.^[15,22,23]

Functioning of neuroglialcytes under the beta-amyloid influence

The neurotoxic beta-amyloid stimulated the production of neurotrophic humoral factors by astrocytes and microglialcytes (up to 207.3% and 126.2% of control values—medium without a toxic agent). Oligodendrocyte function was not affected by beta-amyloid [Figure 3a-c].

It is important to remember that changes in the NSA of supernatants were an indicator integrating the secretion of both stimulators of precursors and inhibitors of their functions, such as proinflammatory cytokines.^[24-26] There is

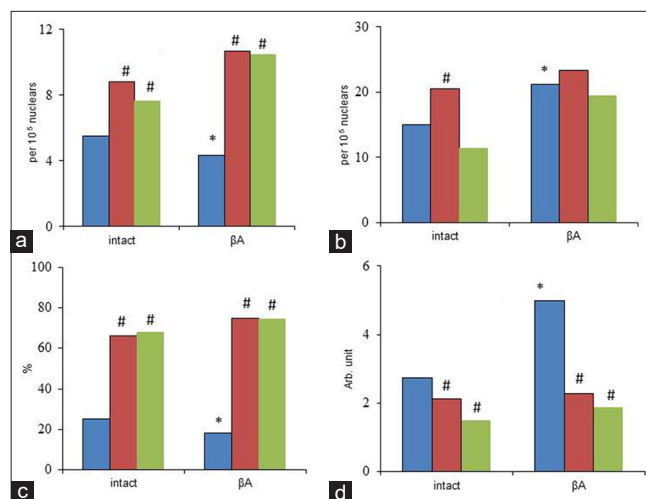


Figure 1: Quantity of neural stem cells: (a) NSC_CFU, (b) NSC_CIFU, (c) in the subventricular zone of the brain; NSC mitotic index, (d) and NSC specialization index. In Figures 1-3: Cellular culture without beta-amyloid (intact) and containing beta-amyloid ($\text{A}\beta$); blue columns – cellular culture without blockers of signaling molecules; red columns – cellular culture with the adenylate cyclase blocker; green columns – cellular culture with the protein kinase A blocker; $P < 0.05$ compared with: *: Cells in the medium without $\text{A}\beta$, #: Cells in the medium without molecule blockers.

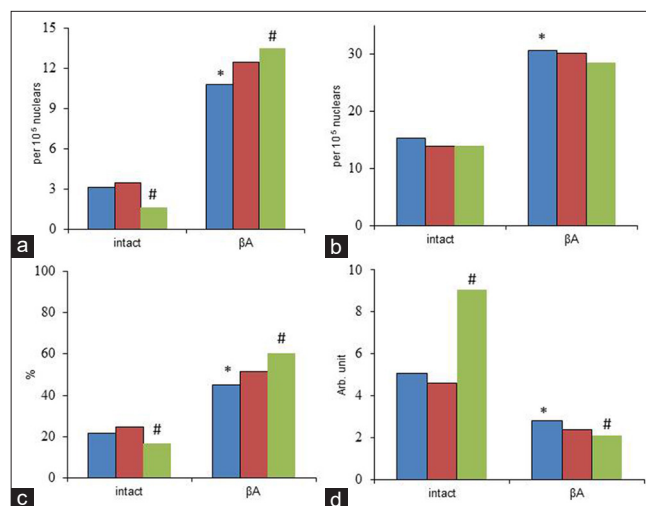


Figure 2: Quantity of neuronal committed progenitors: (a) NCP_CFU, (b) NCP_CIFU, (c) in the subventricular zone of the brain; NCP mitotic index (d) and NCP specialization index; blue columns – cellular culture without blockers of signaling molecules; red columns – cellular culture with the adenylate cyclase blocker; green columns – cellular culture with the protein kinase A blocker; $P < 0.05$ compared with: *: Cells in the medium without $\text{A}\beta$, #: Cells in the medium without molecule blockers.

evidence that beta-amyloid causes a pathologically excessive inflammatory response and is a pathogenic factor in senile dementia.^[2,4]

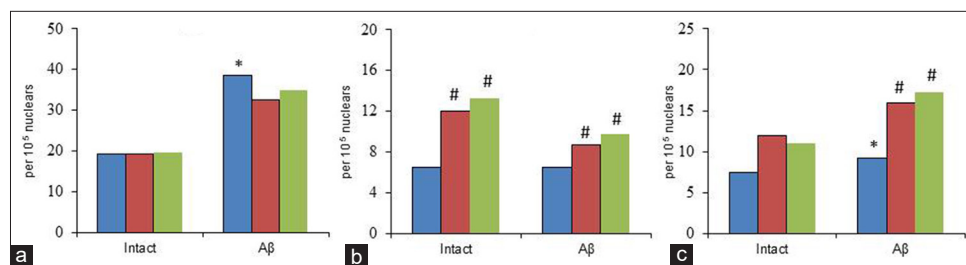


Figure 3: Conditioned media neurosphere stimulating activity (NSA) of neurogliaocytes expressing of (a) astrocyte cell surface antigen-2 (ACSA-2), (b) O4, (c) and CD11b.

Effect of the signalling molecule blockers on the NSC functioning.

The research into the cAMP role in the neuronal progenitor functioning has revealed interesting patterns. The blockers of adenylate cyclase and protein kinase A in cell cultures (both in the presence of beta-amyloid and without it) caused an intensification of progenitor mitosis. The changes in cell culture with beta-amyloid were very pronounced. At the same time, the yield of NSC_CFU was 246.4% and 242.5% of the control (medium with beta-amyloid without inhibitors) when using inhibitors of adenylate cyclase and protein kinase A, respectively [Figure 1a]. The achieved values of this indicator in this case exceeded those in the medium without beta-amyloid. Similar changes were observed in relation to the mitotic activity of NSC [Figure 1c]. Besides, in all cases, there was a decrease in the progenitors' specialisation index. Under conditions of modelling the pathological process, the decrease in the intensity of NSC specialisation was 46.4% and 37.7% when exposed to adenylate cyclase and protein kinase A blockers, respectively [Figure 1d]. This should be considered a factor in improving the processes of neurogenesis by inhibiting aberrant cell development.^[10,14]

Thus, the selective blockade of both signalling molecules stimulated mitosis of multipotent NSCs. Moreover, under conditions of neurotoxic exposure to beta-amyloid, these changes were most pronounced.

Effect of the signalling molecule blockers on the NCP functioning

When studying the influence of adenylate cyclase and protein kinase A blockers on the functions of committed precursors, other regularities were revealed. The impaired cAMP synthesis did not affect the studied NCP parameters, regardless of the neurotoxin content in the culture medium. However, NCP reacted to the protein kinase A blocker. Moreover, in the beta-amyloid-free medium, the amount of NCP_CFU and their mitotic activity in this case decreased (up to 56.4% and 78.3% of the controls) [Figure 2]. Their

maturation accelerated (up to 179.1% of the initial level). Under conditions of neurodegeneration modelling, the NCP response to the protein kinase A inhibitor was different. The blockade of this signalling molecule caused an increase in the yield of NCP_CFU (up to 123.5%) and in the rate of their mitosis (up to 131.7%). At the same time, a decrease in the rate of their specialised development was detected to 74.9% of the control (medium with beta-amyloid) [Figure 2d].

It turns out that the reaction of committed precursors to the protein kinase A blocker was determined by the cultivation conditions. Moreover, when modelling neurodegeneration, this poison activated their growth activity.

Effect of the signalling molecule blockers on neurogliaocytes functioning

The experiments have shown the different effects of selective adenylate cyclase and protein kinase A blockers on the neurogliaocyte functions. The violation of cAMP synthesis and inactivation of protein kinase A in astrocytes did not change the NSA of their supernatants obtained from cells both in the medium with beta-amyloid and without beta-amyloid [Figure 3a]. The blockade of adenylate cyclase and protein kinase A in oligodendrocytes and microgliaocytes caused a marked increase in NSA in conditioned media (both in cell cultures with and without Aβ) [Figure 3b and c]. The levels of humoral stimulators of progenitor functions in supernatants from oligodendrocytes and microgliaocytes during blockade of adenylate cyclase and protein kinase A under intact conditions reached 183.2% and 158.7%, and 201.4% and 149.2%, respectively. The neurodegeneration modelling somewhat reduced the intensity of stimulation of neurotrophin production by O4⁺ cells and, conversely, significantly increased it in CD11b⁺ cells in response to the adenylate cyclase and protein kinase A inactivation [Figure 3].

Thus, disruption of cAMP synthesis, as well as inactivation of protein kinase A, stimulated oligodendrocytes and microgliaocytes, including under conditions of the neurotoxic effect of beta-amyloid.

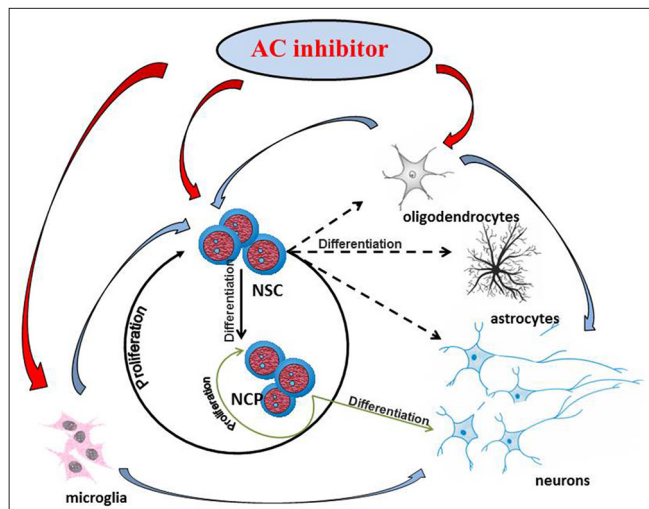


Figure 4: Synchronisation of cells involved in regeneration activity under the influence of the adenylate cyclase blocker under conditions of the neurotoxic effects of beta-amyloid. Figures 4 and 5: Uninterrupted lines are activation; broken lines are inhibition; broad blue arrows are the neurotrophic effects of neurogliaocytes and broad red arrows are the activating effect of signal molecule blockers. AC: Adenylate cyclase, NSC: Neural stem cells, NCP: Neuronal committed progenitors

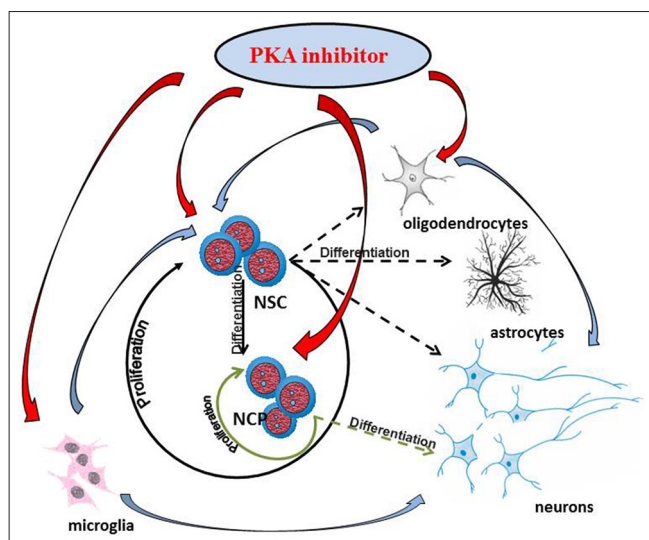


Figure 5: Synchronisation of cells involved in regeneration activity by the protein kinase A blocker under conditions of the neurotoxic effects of beta-amyloid. NSC: Neural stem cells, NCP: Neuronal committed progenitors, PKA: Protein kinase A

DISCUSSION

The findings confirm the data on discoordination of multipotent and unipotent progenitor cells under the neurotoxic effects of beta-amyloid conditions.^[5,10,11,27] Inhibition of the proliferative activity of NSC with an increase in that of NCP was revealed. The intensification

of the specialised development of NSC increased, while in committed precursors, on the contrary, it decreased. In addition, it is important that these various changes in the mitotic activity of progenitors were recorded when the coupling of their processes of proliferation and specialisation was disrupted. At the same time, the detected extremely rapid differentiation of NSCs is likely the cause of the aberrant development of nerve cells due to beta-amyloid.^[15,22,23] These phenomena of the response of the brain cellular renewal system to a neurotoxic agent will necessarily affect the effectiveness of neuroregeneration in AD.^[28,29] Simultaneously, the contribution of individual types of neurogliaocytes to the development of the detected discoordination of the functions of NSC and NCP remains unclear.^[14,30,31] It is possible that the increase in the secretion of humoral stimulants by astrocytes and microgliaocytes under the influence of the neurotoxin is excessive (including the reason for the high intensity of NSC specialisation). In this case, their reaction is decompensatory and is involved in the dysregulation of the cell renewal system.^[30,32] In addition, hyperproduction of tau proteins, disadaptation of the cholinergic system and many other changes in the homeostasis of nervous tissue during the development of dementia^[33,34] will only enhance and aggravate dysregeneration. Based on this, the development of a pharmacological concept for synchronising the activity of various types of CIR seems to be a very attractive method for stimulating neuroregeneration and neuroplasticity in AD.

At the same time, it has been established that cAMP (including through protein kinase A) under the influence of a specific neurotoxin further inhibits the progression of the NSC cell cycle and activates their development. However, only protein kinase A-dependent signalling plays a role in the new pattern of NCP function. It is likely that these changes in signal transduction in precursors under the influence of beta-amyloid represent a key mechanism for maladaptation of the cellular renewal system of the brain in AD.^[17,18,35]

Furthermore, the experimental results demonstrate the unique prospect of coordinating the progenitor functioning by targeting cAMP-dependent pathways.^[10,12] Stimulation of NSC proliferation and the coupling of this process with their specialisation under the influence of adenylate cyclase and protein kinase A blockers has been demonstrated [Figures 4 and 5]. But with regard to NCP, the PKA inhibitor turned out to be the most acceptable corrector. It is also important that this targeting of signal transduction, based on the study data, does not cause a negative impact on the secretory function of neurogliaocytes. Inactivation of adenylate cyclase and protein kinase A somewhat reduced the severity of the neurotrophin production ability of oligodendrocytes (which, as noted earlier, could be excessive) and, on the contrary, significantly increased the supernatant NSA from microglial cells (apparently due to

blockade of the secretion of pathogenic proinflammatory cytokines).^[1,25,26]

CONCLUSION

The results obtained give grounds to consider the development of an advanced concept for the pharmacotherapy of AD using adenylate cyclase and protein kinase A blockers promising. However, based on these experiments, PKA is a more promising target for potentially fundamentally novel medicines.

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Declaration of patient consent: Patient's consent was not required as there are no patients in this study.

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