Research Results in Pharmacology

Research Results in Pharmacology 5(2): 71–77
UDC: 615.225 [616.831-005]
DOI 10.3897/rrpharmacology.5.35392

Research Article

New cerebrovascular agent with hypotensive activity

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Academic editor: *Oleg Gudyrev* ♦ **Received** 11 April 2019 ♦ **Accepted** 18 May 2019 ♦ **Published** 27 June 2019

Citation: Kim GA, Gan'shina TS, Kurza EV, Kurdyumov IN, Maslennikov DV, Mirzoian RS (2019) New cerebrovascular agent with hypotensive activity. Research Results in Pharmacology 5(2): 71–77. https://doi.org/10.3897/rrpharmacology.5.35392

Abstract

Introduction: In cerebrovascular disorders, special attention is paid to a hypertensive cerebrovascular crisis, which combines a vascular injury of the brain and hypertension. The paper studies the cerebrovascular properties of the calcium channel blocker of S-Amlodipine nicotinate antihypertensive agent.

Materials and methods: Tests were performed on 96 nonlinear male rats, measuring local blood flow in the cerebral cortex in 36 awake animals, using a laser Doppler flowmeter. Cerebral circulation was recorded in the animals when modeling ischemic and hemorrhagic brain injuries.

Results and discussion: S-Amlodipine nicotinate (0.1 mg/kg i/v) shows a pronounced cerebrovascular activity in the models of ischemic and hemorrhagic injuries of the brain. In terms of the vasodilating effect in ischemic brain injury, the drug is comparable to mexidol, nimodipine, picamilon, but is superior to nimodipine and picamilon in terms of duration of action, and in the model of hemorrhagic stroke, S-Amlodipine nicotinate is superior to nimodipine and is comparable to picamilon and mexidol. The analysis of the mechanism of action of the agent revealed the participation of $GABA_A$-receptors in the implementation of cerebrovascular properties of the agent.

Conclusion: Significant cerebrovascular activity of S-Amlodipine nicotinate (0.1 mg/kg i/v) antihypertensive agent was revealed. The presence of GABAergic mechanism on cerebral blood flow in the agent action along with blockade of slow calcium channels ensures its high efficacy in treatment of both ischemic and hemorrhagic brain injuries.

Keywords

S-Amlodipine nicotinate, mexidol, nimodipine, picamilon, bicuculline, global transient ischemia, hemorrhagic stroke model, cerebral circulation.

Introduction

Cerebrovascular diseases are among the leading causes of death and disability of the population of the Russian Federation and other countries (Benjamin et al. 2019, Skvortsova et al. 2018). Currently, restoration of blood supply to the affected area of the brain for the rapid supply of oxygen and glucosein is a generally recognized strategy in the treatment of patients with ischemic cerebrovascular disorders. This is shown by the high efficacy of reperfusion therapy which includes a combination of systemic thrombolysis and mechanical thrombectomy using stent retrievers (Lee 2017, Skvortsova et al. 2018). Vasoactive agents are widely used in neurological practice, such as

mexidol (Tanashyan et al. 2012, Voronina 2000), picamilon (Gusev et al. 2018, Mirzoyan et al. 2018) and a calcium channel blocker nimodipine (Nishizawa et al. 2008, Scriabine and van den Kerckhoff 1988), which possess significant cerebrovascular antiischemic activity (Mirzoyan et al. 2018).

It is well-known that an inhibitory neurotransmitter – GABA – is also involved in the regulation of cerebral circulation, dilating cerebral vessels as a result of interaction with $GABA_A$-receptors located in the vessels (Krause et al.1980, Mirzoyan et al. 1970, Napoleon et al. 1987). In the ischemic brain injury, the balance between inhibitory GABAergic and stimulating glutamatergic systems is disturbed in the central nervous system. In this case, an excess amount of glutamate is formed in the brain tissue, which is released and triggers a complex cascade of neurotoxic processes that leads to the death of nervous tissue (Lai et al. 2014). To prevent this process and reduce the neurotoxic effect of glutamate, either a blockade of glutamate receptors or activation of GABAergic neurotransmission in the brain is necessary (Green et al. 2000, Liu et al. 2013, Schwartz-Bloom and Sah 2001, Sorokina et al. 2002). It is indicative that both mexidol and picamilon show their greatest cerebrovascular reactivity in cerebral ischemic injuries and this effect is eliminated or offset by specific blockers of $GABA_A$-receptors (Gnezdilova et al. 2010, Silkina et al. 2005). Thus, agents with a GABAergic component in the mechanism of action in the cerebral ischemic injury, by activating the GABAergic system, contribute to the restoration of balance between inhibitory and excitatory processes in the central nervous system.

In cerebrovascular disorders, special attention is paid to a hypertensive cerebrovascular crisis, which combines a vascular injury of the brain and hypertension. Such patients are prescribed complex therapy, consisting of agents that affect both cerebral circulation and blood pressure.

Therefore, looking for and studying new agents with pronounced cerebrovascular and hypotensive activity to treat patients with cerebrovascular diseases combined with hypertensive conditions, is an urgent task of modern pharmacology. In this aspect, the main focus of the present study was an antihypertensive agent – S-Amlodipine nicotinate (Kim et al. 2008).

The aim of the study was a comparative study of the influence of S-Amlodipine nicotinate, amlodipine besylate on blood pressure and of the above-mentioned salts of amlodipine, as well as mexidole, nimodipine and picamilon on cerebral blood flow and blood pressure in ischemic and hemorrhagic injuries of the brain with the analysis of the mechanism of their cerebrovascular effect.

Materials and methods

The study was performed on 132 nonlinear male rats weighing 250–300 g, including 96 anesthetized (with chloral hydrate, 400 mg/kg, or urethane, 1300 mg/kg, intraperitoneally) and 36 awake animals. The experiments were carried out in compliance with the ethical rules of animal welfare, approved by the Ethical Committee of Zakusov Institute of Pharmacology.

Blood pressure was recorded in awake rats in the caudal artery. Systolic blood pressure was measured with NIBP 200A device by BIOPAC System Inc. (small animal tail noninvasive blood pressure system) before administration of the agent or distilled water and 1, 2, 4, 6 and 24 hours after administration. Heart rate was determined by the number of pulses per minute on the electrocardiogram in the 2nd lead. Respiration rate was determined by the number of animal breaths per minute. Registration of local cerebral blood flow in the parietal cortex of rats was performed with an ALF-21 laser Doppler flowmeter by Transonic System Inc. (USA). At the same time, changes in the level of blood pressure in the femoral artery were recorded. All measurements were recorded with a polygraph by BIOPAC (USA), and the recording was performed digitally on a personal computer.

To assess changes in regional cerebral blood flow in rats, blood flow to the brain in the internal carotid artery was recorded using a T106 ultrasonic volume flowmeter by Transonic System Inc. (USA). The sensor was installed on the common carotid artery in rats after ligation of its outer branch.

Global transient ischemia was induced in rats by occlusion using clamps on both common carotid arteries for 10 minutes with simultaneous reduction of blood pressure by bloodletting to 40–50 mm Hg. Ten minutes later, the clamps were removed, and the blood was reinfused. The substances were administered 40–45 minutes after global transient brain ischemia after hemodynamic parameters had stabilized.

Simulation of intracerebral haemorrhage was performed in anesthetized rats in a stereotaxic apparatus according to the method by A.N. Makarenko et al. (2002). With the help of a special device (mandren-knife), the destruction of brain tissue in the area of the internal capsule was carried out, followed (2–3 minutes later) by the introduction of arterial blood which had been taken from the femoral artery of the animal into the injured zone. The agents were administered 40 minutes after all the procedures.

Statistical data processing was performed using Statistica 8.0 software package (StatSoft, USA). The data is presented as a median. The confidence level of $p \leq 0.05$ was considered statistically significant.

A radioreceptor analysis of the impact of the substances on the specific binding of [^{3}H]-SR 95531 (gabazine) was performed according to the modified methods in vitro, using membrane preparations containing $GABA_A$-receptors in the frontal cortex of rats (Hawkinson et al. 1996). Radioactivity of each sample was measured with a Tri-Carb 2900 TR (Perkin Elmer) scintillation counter with a counting efficiency of 42–45%. The results were processed using GraphPad Prism 5.0 software.

The study used the following substances: S-Amlodipine nicotinate (by ECOCHEM-INNOVATIONS LLC to the order of Consortium-PIK LLC, Russia); amlodipine

besylate (by Shanghai Rokem International Trading Co., Ltd., China); nimodipine (by BayerAG, Germany); mexidol (service division of Zakusov Institute of Pharmacology, Russia); picamilon (by Pharmstandard, Russia), which were administered through a polyethylene catheter into the femoral vein of animals.

Results and discussion

Study of the effect of S-Amlodipine nicotinate and amlodipine besylate on the blood pressure of awake rats

The study started with examination of antihypertensive properties of S-Amlodipine nicotinate versus amlodipine besylate. The agents were studied in two doses – 5 and 10 mg/kg with intragastric administration (per os). The study showed that S-Amlodipine nicotinate causes a decrease in blood pressure in awake rats (n=10) by an average of 40 % of the baseline. Hypotensive effect of the agent at this level is maintained for 6 hours. After 24 hours, the pressure level remains low and averages 26% of the baseline. The reference agent – amlodipine besylate at a dose of 10 mg/kg in awake rats (n=10) – causes a decrease in blood pressure levels as soon as 1 hour later on average by 16%, i.e. it is inferior to S-Amlodipine nicotinate in efficiency (40%, $p<0.05$).

The experiments showed that distilled water had no effect on the systolic pressure of the studied animals (n=10). The pressure level was about 100 mm Hg throughout the experiment.

The study showed that S-Amlodipine nicotinate did not cause significant changes in either respiration rate or heart rate in the experimental animals throughout the experiment.

Thus, the study of the effect of S-Amlodipine nicotinate in comparison with that of amlodipine besylate on the level of blood pressure in awake rats made it possible to establish that S-Amlodipine nicotinate in awake rats significantly exceeded amlodipine besylate in terms of the amplitude and duration of the effect (Gan'shina et al. 2014).

The influence of S-Amlodipine nicotinate, amlodipine besylate, mexidol, picamilon, and nimodipine on cerebral blood flow in global transient cerebral ischemia

Given the cerebrovascular activity of nicotinic acid, which is part of S-Amlodipine nicotinate, it was interesting to study the effect of the agent on cerebral circulation. The experiments showed that S-Amlodipine nicotinate at a dose of 0.1 mg/kg 10 minutes after intravenous administration caused an increase in cerebral blood flow in the carotid artery system by an average of 64.5% (n=10). The effect of the agent persisted for 60 minutes or longer. Ten minutes after administration of the agent, the level of blood pressure in these experiments decreased by an average of 32%. The hypotensive effect persisted until the end of the experiment. The effect of amlodipine besylate was also studied in regional cerebral blood flow, at a dose of 0.1 mg/kg with intravenous administration. The experiments showed that amlodipine besylate caused a small statistically insignificant increase in cerebral blood flow after 10 minutes in 7 experiments out of 10. The hypotensive effect of the agent persisted throughout the experiment.

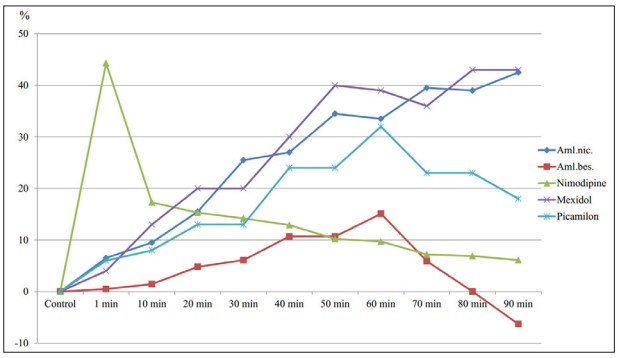

Figure 1. Effect of S-Amlodipine nicotinate (Aml.nic., 0.1 mg/kg, i/v), amlodipine besylate (Aml.bes., 0.1 mg/kg, i/v), nimodipine (0.03 mg/kg, i/v), mexidol (200mg/kg, i/v) and picamilon (50mg/K, i/v) on the local blood flow (%) in the cerebral cortex of rats after global transient ischemia.

The experiments showed that S-Amlodipine nicotinate (0.1 mg/kg, i/v) in the anesthetized rats in global transient ischemia immediately after administration caused an increase in local cerebral blood flow, which by the 90th minute was 42.5% (n=10) of the control level (Fig. 1). In ischemic brain damage, S-Amlodipine nicotinate causes a gradually developing and by the end of the experiment significant decrease in blood pressure by an average of 6.6%.

In the study of the effect of amlodipine besylate (0.1 mg/kg, i/v) on the local cerebral blood flow in rats in global transient ischemia, it was shown that the agent caused a small slowly progressing increase in the blood flow in the cerebral cortex of rats, which by the 40th minute after administration of the agent was on average 10.7% (n=10) (Fig. 1).

Then the blood flow returned to the baseline, and by the end of the experiment there was a slight decrease. The level of blood pressure under the influence of amlodipine besylate gradually decreased by 8.2% 10 minutes after its administration. The hypotensive effect of amlodipine besylate increased throughout the observation period and by the end of the experiment averaged 25.7%.

Thus, S-Amlodipine nicotinate improves blood supply to the rat brain in the condition of its ischemic lesion, associated with developing hypotension, and by its cerebrovascular anti-ischemic activity it significantly exceeds amlodipine besylate (42.5% and 16%; $p<0.05$).

Mexidol, as a reference agent, in rats at a dose of 200 mg/kg with intravenous administration after global transient ischemia, in contrast to intact animals, causes a gradual increase in local cerebral blood flow in the cortex of animals, which at the 90th minute is an average of 43% (n=11) (Fig. 1).

Picamilon (50 mg/kg i/v), administered 40 min after global transient ischemia in anesthetized rats, also causes a gradual increase in local cerebral blood flow, which by the 50th minute reaches an average of 32% (n=10) (Fig. 1). At

similar intervals, under the influence of picamilon, there is a decrease in blood pressure, which by the 90th minute after administration of the agent is 18% of the initial level.

Nimodipine in experiments with global transient ischemia in animals immediately after intravenous administration at a dose of 0.03 mg/kg causes an increase in local blood flow in the cerebral cortex of rats by an average of 44.3% (n=10). However, after 10 minutes, the effect of nimodipine wears off, averaging 17.3%, and remains at this level until the end of the experiment (Fig. 1). Nimodipine in animals with global transient brain ischemia causes a decrease in blood pressure by an average of 39.6% (during the 1st minute) and 17% (10 minutes or more).

Thus, S-Amlodipine nicotinate causes a significant increase in local cerebral blood flow in rats with global transient brain ischemia, i.e. has a pronounced cerebrovascular anti-ischemic effect. The amplitude of the vasodilator effect of the agent is comparable to mexidol, nimodipine, picamilone and superior to amlodipine besylate in terms of the effect amplitude, and to nimodipine and picamilon in terms of the effect duration.

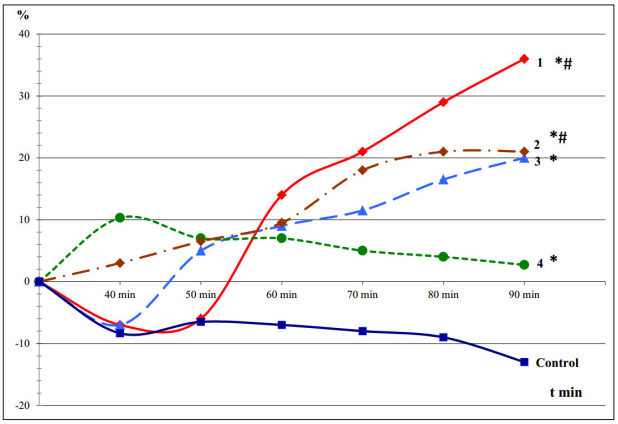

Figure 2. Effect of S-Amlodipine nicotinate (1), picamilon (2), mexidol (3) and nimodipine (4) on local blood flow (%) in the cerebral cortex of rats 30 min (background) after hemorrhagic injury. Control – changes in hemorrhagic brain injury. *Note*: * – $p<0.05$ between the agent and control, # – $p<0.05$ between S-Amlodipine nicotinate and picamilon with nimodipine.

The influence of S-Amlodipine nicotinate, mexidol, picamilon and nimodipine on cerebral blood flow in the model of brain hemorrhagic injury

The experiments showed that hemorrhagic injury to the internal capsule of the brain caused a significant decrease in the level of cerebral blood flow in the cerebral cortex of rats in both ipsilateral and contralateral hemispheres. The level of local cerebral blood flow decreased immediately after the simulation of hemorrhagic stroke, after 30 minutes was an average of 27% of the baseline ($p<0.05$), then the blood flow continued to decrease and by the 90th minute was 40% (n=10). After hemorrhagic brain injury, multidirectional changes in blood pressure were observed. The level of blood pressure generally reduced by an average of 12%. The absence of a direct link between changes in cerebral blood flow and blood pressure indicates that the decrease of blood supply to the brain was due to a significant constrictor reaction of cerebral vessels. The studied substances were administered 30 minutes after the procedure of hemorrhagic injury.

The experiments showed that S-Amlodipine nicotinate (0.1 mg/kg i/v) in the model of hemorrhagic stroke after a slight decrease in cerebral blood flow caused its increase, which by the 40–60th minutes was an average of 36% (n=10), i.e. restored blood flow to the baseline (Fig. 2). It should be noted that in these conditions, under the influence of S-Amlodipine nicotinate, a certain decrease in blood pressure by the 40–60th minutes after administration was followed by a slight 14%.increase.

Mexidol at a dose of 200 mg/kg when administered intravenously to anesthetized rats in the simulation of hemorrhagic stroke causes a gradual increase in local blood flow in the cerebral cortex of rats, which by the 60th minute after administration of the agent averaged to 20 % of the baseline (n=10) (Fig. 2). The level of blood pressure

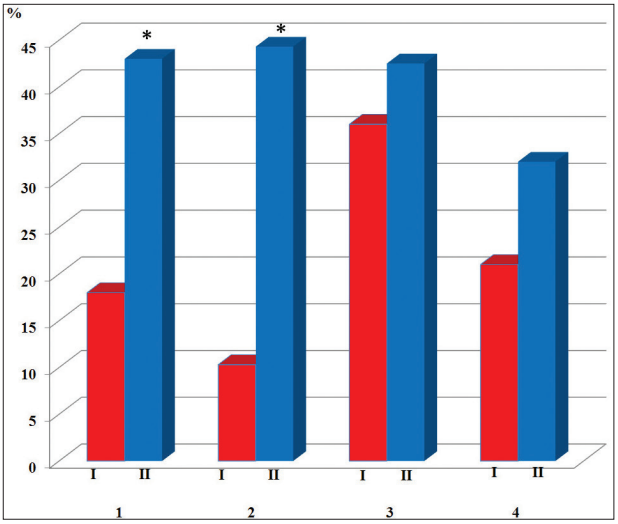

Figure 3. Effect of mexidol (1), nimodipine (2), S-Amlodipine nicotinate (3) and picamilon (4) on changes in local blood flow (%) in rat cerebral cortex in the model of hemorrhagic stroke (I) and after global transient ischemia (II). *Note*: * – $p<0.05$ – between ischemic and hemorrhagic brain injuries.

reduced by the 10th minute by an average of 10 %, and then restored to the initial level.

Picamilon, when administered 30 minutes after hemorrhagic brain injury at a dose of 50 mg/kg intravenously, causes a slowly progressing increase in local cerebral blood flow, which by the 50th minute of observation is an average of 21 % (n=10) (Fig. 2). Blood pressure in these conditions does not undergo significant changes.

Nimodipine (0.03 mg/kg i/v), after hemorrhagic brain damage by the 10th minute after administration, causes a slight increase in local blood flow by an average of 10.3 % (n=9) (Fig. 2). Then the blood flow gradually decreases and reaches the baseline by the 60th minute. Blood pressure immediately after administration of the agent

decreases by 13%, which quickly recovers and does not undergo significant changes throughout the experiment.

Therefore, S-Amlodipine nicotinate increases blood flow to the brain in the model of hemorrhagic stroke. The amplitude of the cerebrovascular effect of the agent is superior to that of nimodipine and is comparable with that of picamilon and mexidol.

The results of the last two sections are summarized in Figure 3, which shows that a statistically significant difference in the cerebrovascular effects of mexidol and nimodipine was revealed when they were studied in ischemic and hemorrhagic brain injuries, i.e. in hemorrhagic lesion, the vasodilating activity of the agents is significantly weakened.

A different picture is observed in the comparative study of S-Amlodipine nicotinate and picamilon. These drugs improve the blood supply to the rat brain to the same extent both in ischemic and hemorrhagic injuries (Mirzoyan et al. 2018).

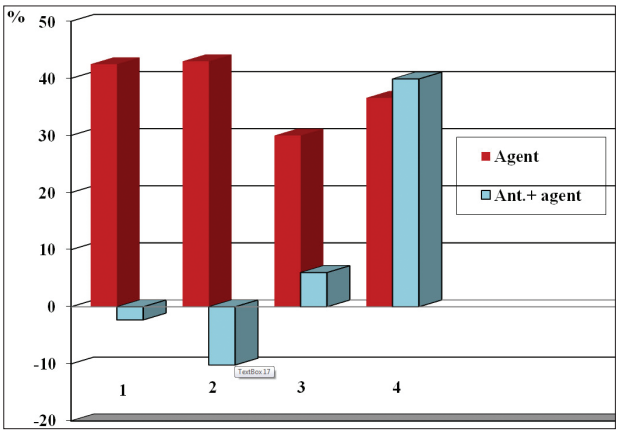

Figure 4. The effect of S-Amlodipine nicotinate (1), mexidol (2), picamilon (3) and nimodipine (4) on the blood supply to the brain of rats in global transient ischemia (the agent) and against the effect of the antagonists of the GABA$_A$-receptor (Ant.+ agent).

Analysis of anti-ischemic cerebrovascular effect of S-Amlodipine nicotinate, mexidol, picamilon and nimodipine

Taking into account the crucial role of GABAergic mechanisms in the regulation of cerebral circulation, the influence of pharmacological agents on the local cerebral blood flow of rats subjected to global transient ischemia and after the preliminary introduction of a specific GABA$_A$-receptor blocker – bicuculline (0.5 mg/kg; n=8) – was studied. The experiments showed that in these conditions, S-Amlodipine nicotinate did not cause significant changes in local cerebral blood flow, whereas in control experiments blood flow increased by an average of 42.5 % (Fig. 4). The data obtained point at the GABAergic mechanism of the cerebrovascular anti-ischemic effect of the agent.

When studying the mechanism of cerebrovascular effect of mexidol (200 mg/kg, i/v), it was shown that 10 minutes after its administration in ischemic conditions and under the influence of bicuculline, local cerebral blood flow in most experiments decreased by an average of 10.2 % (control: 43 %). Blood pressure under the influence of mexidol in these conditions also reduced by an average of 17.3 % (Gnezdilova et al. 2010). These data indicate that GABA$_A$-receptors participated in the implementation of vasodilator effect of the drug (Fig. 4).

To clarify the mechanism of the cerebrovascular effect of picamilon, its effect on local cerebral blood flow was studied under the influence of the GABA$_A$-receptor blocker – picrotoxin (0.5 mg/kg, i/v). It turned out that in these conditions the agent increased cerebral blood flow by only 6.0 % (control: 32 %), i.e. to a much lesser extent than in the control (Silkina et al. 2005). Consequently, the cerebrovascular effect of picamilon is mediated through the chlorine channel of the GABA$_A$-receptor (Fig. 4).

Nimodipine exhibits vasodilator activity both in ischemic brain damage, and against the influence of the

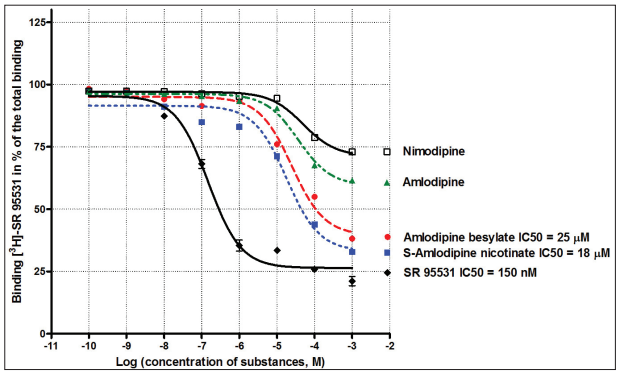

Figure 5. Effect of S-Amlodipine nicotinate, amlodipine besylate, amlodipine (base) and nimodipine on GABA$_A$-receptors in rat brain *in vitro*. *Note*: Along Y axis – the degree of specific ligand binding [^{3}H]-SR 95531. Along X axis – the concentration of substances in mol/l.

antagonist GABA$_A$-receptors of bicuculline in global transient ischemia (n=8). Consequently, GABAergic mechanisms are not involved in the implementation of the cerebrovascular effect of nimodipine (Fig. 4).

The obtained data became the basis for a detailed study of the role of GABA system in the detected effects of S-Amlodipine nicotinate. In particular, the ability of S-Amlodipine nicotinate to interact directly with GABA$_A$-receptors using rat brain membranes (n=6) was studied in a series of experiments by in vitro radioligand analysis. In similar conditions, amlodipine besylate, amlodipine (base) and nimodipine were also studied. It was found that S-Amlodipine nicotinate competed for specific binding sites [^{3}H]-SR 95531 (gabazine) with IC_{50}=18 μm. Amlodipine besylate (IC_{50}=25μm) showed a close degree of affinity to GABA$_A$-receptors, while amlodipine (base) and nimodipine were inactive (IC_{50}>1 mM) (Fig. 5). Therefore, unlike nimodipine, only salts of amlodipine and, to a greater extent, of S-Amlodipine nicotinate interact with GABA$_A$-receptors of brain tissues (Kim et al. 2017).

Conclusion

The study showed that S-Amlodipine nicotinate is superior to amlodipine besylate in efficacy and duration of the hypotensive effect, which corresponds to the literature data (Kim et al. 2008).

In terms of cerebral ischemia, S-Amlodipine nicotinate in its cerebrovascular effect is comparable to mexidol, nimodipine and picamilon, but exceeds nimodipine and picamilon in terms of duration of the effect.

In hemorrhagic brain injury, S-Amlodipine nicotinate in its vasodilator effect is superior to nimodipine and is comparable to mexidol and picamilon. The presence of the GABAergic component in the mechanism of S-amlodipine action in combination with blockade of the slow calcium channels ensures its high efficacy in treatment of both ischemic and hemorrhagic brain injuries.

Therefore, it is promising to further expand the preclinical study of S-Amlodipine nicotinate with a view to its subsequent clinical study and implementation in neurological practice. The ability of S-Amlodipine nicotinate to dilate the vessels of the brain in both ischemic and hemorrhagic injuries makes it worthwhile to study the agent in conditions where cerebrovascular diseases are combined with hypertension: in hypertensive cerebral crisis, hemorrhagic brain injuries in the period of angiospasm and hypertension, with neurosurgical surgical interventions, including surgical treatment of hemorrhagic stroke.

References

- Benjamin EJ, Munther P, Alonso A, Bittencourt MS, Callaway CW, Carson AP et al. (2019) Heart disease and stroke statistics – 2019 update: a report from the American Heart Association. Circulation 139(10): e56–e528. https://doi.org/10.1161/CIR.0000000000000659 [PubMed]
- Gan'shina TS, Kim GA, Gnezdilova AV, Gorbunov AA, Mirzoyan RS (2014) Comparative study of the effect of S-anlodipine nicotinate and amlodipine besylate on the arterial pressure of awake rats. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 77(8): 20–22. [PubMed]
- Gnezdilova AV, Gan'shina TA, Mirzoyan RS (2010) GABAergic mechanism of cerebrovascular effect of mexidol. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 73(10): 11–13. [PubMed]
- Green AR, Hainsworth AH, Jackson DM (2000) GABA potentiation: a logical pharmacological approach for the treatment of acute ischemic stroke. Neuropharmacology 39(9): 1483–1494. https://doi.org/10.1016/S0028-3908(99)00233-6 [PubMed]
- Gusev EI, Chukanova EI, Chukanova AS (2018) Chronic Cerebrovascular Insufficiency (Risk Factors, Pathogenesis, Clinic, Treatment). AST 345 Ltd., Moscow, 189 pp.
- Hawkinson JE, Acosta-Burruel M, Kimbrough CL, Goodnough DB, Wood PL (1996) Steroid inhibition of [3H] SR 95531 binding to the GABAA recognition site. European Journal of Pharmacology 304(1–3): 141–146. https://doi.org/10.1016/0014-2999(96)00090-8 [PubMed]
- Kim GA, Gan'shina TS, Vasil'eva EV, Kovalev GI, Kurza EV, Maslennikov DV, Mirzoyan RS (2017) $GABA_A$ receptor mechanism of antiischemic cerebrovascular effect of S-Amlodipine nicotinate. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 80(5): 7–10.
- Kim SA, Park S, Chung N, Lim DS, Yang JY, Oh BH, Tahk SJ, Ahn TH (2008) Efficacy and safety profiles of a new S(-)-amlodipine nicotinate formulation versus racemic amlodipine besylate in adult Korean patients with mild to moderate hypertension: an 8-week, multicenter, randomized, double-blind, double-dummy, parallel-group, phase III, noninferiority clinical trial. Clinical Therapeutics 30(5): 845–857. https://doi.org/10.1016/j.clinthera.2008.05.013 [PubMed]
- Krause DN, Wong E, Degener P, Roberts E (1980) GABA receptors in bovine cerebral blood vessels: binding studies with [3H]muscimol. Brain Research 185(1): 51–57. https://doi.org/10.1016/0006-8993(80)90669-1 [PubMed]
- Lai TW, Zhang S, Wang YT (2014) Excitotoxicity and stroke: Identifying novel targets for neuroprotection. Progress in Neurobiology 115: 157–188. https://doi.org/10.1016/j.pneurobio.2013.11.006 [PubMed]
- Lee S-H (2017) Pathophysiology of ischemic stroke. In: Pack J (Eds) Acute Ischemic Stroke (Medical, Endovascular and Surgical Techniques), Springer, Singapore, 3–26. https://doi.org/10.1007/978-981-10-0965-5_1
- Liu W, Xu Z, Deng Y, Xu B, Wei Y, Yang T (2013) Protective effects of memantine against methylmercury-induced glutamate dyshomeostasis and oxidative stress in rat cerebral cortex. Neurotoxicity Research 24(3): 320–337. https://doi.org/10.1007/s12640-013-9386-3 [PubMed]
- Makarenko AN, Kositsin NS, Svinov MM (2002) Simulation of local cerebral hemorrhage in different brain structures of experimental animals. I.P. Pavlov Journal of Higher Nervous Activity [Zhurnal Vysshey Nervnoy Deyatel'nosti] 52(6): 765–768. [PubMed] [in Russian]
- Mirzoyan RS, Gan'shina TS, Kim GA, Kurdyumov IN, Maslennikov DV, Kurza EV (2018) Pharmacological correction of cerebrovascular disorders in various experimental pathological conditions. Annals of Clinical and Experimental Neurology [Annaly Klinicheskoy i Experimental'noy Nevrologii] 12(1): 31–37. https://doi.org/10.25692/ACEN.2018.1.5. [in Russian]
- Mirzoyan SA, Kazaryan BA, Akopyan VP (1970) Decarcoxylase activity of glutamic acid in the vessels of the brain. Proceedings of the USSR Academy of Sciences [Doklady Akademii Nauk SSSR] 190(5): 1241–1243. [in Russian]
- Napoleone P, Erdö S, Amenta F (1987) Autoradiographic localization of the GABAA-receptor agonist [3H]muscimol in rat cerebral vessels. Brain Research 423(1–2): 109–115. https://doi.org/10.1016/0006-8993(87)90830-4 [PubMed]
- Nishizawa S (2008) Vasospasm biochemistry in cerebral vasospasm. In: Kiris T, Zhang JH (Eds) New Strategies in Research and Treatment. Actan Neurochirurgica, Springer-Verlag. Supp.104: 55–58. https://doi.org/10.1007/978-3-211-75718-5_10
- Schwartz-Bloom RD, Sah R (2001) Gamma-Aminobutyric acid(A) neurotransmission and cerebral ischemia. Journal of Neurochemistry 77(2): 353–371. https://doi.org/10.1046/j.1471-4159.2001.00274.x [PubMed]

- Scriabine A, van den Kerckhoff W (1988) Pharmacology of nimodipine: a review. Annals of the New York Academy of Sciences 522: 698–706. https://doi.org/10.1111/j.1749-6632.1988.tb33415.x [PubMed]
- Silkina IV, Ganshina TS, Seredenin SB, Mirzoyan RS (2005) GABA-ergic mechanism of cerebrovascular and neuroprotective effects of afobazole and picamilon. Experimental and Clinical Pharmacology [Eksperimental'naia i Klinicheskaia Farmakologiia] 68(1): 20–24. [in Russian]
- Skvortsova VI, Shetova IM, Kakorina EP, Kamkin EG, Boyko EL, Dashyan VG, Krylov VV (2018) Healthcare system for patients with stroke in Russia. Results of 10-years implementation of the measures aimed at improvement of medical care for patients with acute cerebrovascular events. Annals of Clinical and Experimental Neurology [Annaly Klinicheskoy i Experimental'noy Nevrologii] 12(3): 5–12. https://doi.org/10.17116/jnevro2018118415-12 [in Russian]
- Sorokina ND, Selitskii GV, Kositsyn NS, Svinov MM (2002) Neurobiologycal problems of brain ischemia and post stroke epilepsy. I.P. Pavlov Journal of Higher Nervous Activity [Zhurnal Vysshey Nervnoy Deyatel'nosti] 52(6): 656–664. [PubMed] [in Russian]
- Tanashyan MM, Lagoda OV, Antonova KV (2012) Chronic cerebrovascular diseases associated with metabolic syndrome: new treatment approaches. S.S. Korsakov Journal of Neurology and Psychiatry [Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova] 11: 21–26.
- Voronina TA (2000) Hypoxia and memory. Features of the effects and use of nootropic drugs. Annals of the Russian Academy of Medical Sciences [Vestnik Rossiiskoi Akademii Medetsinskikh Nauk] 9: 27–34.

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