Research Results in Pharmacology

Research Results in Pharmacology 7(3): 73–81
UDC: 612.17+612.8+612.2
DOI 10.3897/rrpharmacology.7.75337

Research Article

Role of indole derivative SS-68 in increasing the frequency range of cardiac rhythm control (reflex stimulation of the sinoatrial node)

Pavel A. Galenko-Yaroshevsky[1,3], Anatoly A. Nechepurenko[2], Tatiana G. Pokrovskaya[3], Nikolai L. Shimonovsky[4], Alexander S. Dukhanin[4], Konstantin F. Suzdalev[5], Polina D. Maslova[1], Natalia M. Makhnova[1], Vadim V. Shneivais[1], Valery G. Abushkevich[1], Anait V. Zelenskaya[1], Valeria V. Seletskaya[1], Saida K. Ahedzhak-Naguse[1], Konstantin G. Korotkov[6]

1 *Kuban State Medical University, 4 Mitrofan Sedin St., Krasnodar 350063, Russia*
2 *Federal Center for Cardiovascular Surgery, 4 Pokrovskaya Roscha St., Astrakhan 414011, Russia*
3 *Research Institute of Pharmacology of Living Systems, Belgorod State National Research University, 85 Pobedy St., Belgorod 308015 Russia*
4 *Pirogov Russian National Research Medical University, 1 Ostrovitjanova St., Moscow 117997, Russia*
5 *Southern Federal University, 105/42 Bolshaya Sadovaya St., Rostov-on-Don 344006, Russia*
6 *Saint Petersburg Research Institute of Physical Culture, 56E Ligovsky Prospekt, St. Petersburg 191040, Russia*

Corresponding author: Pavel A. Galenko-Yaroshevsky (Galenko.Yarochevsky@gmail.com)

Academic editor: Oleg Gudyrev ♦ **Received** 15 May 2021 ♦ **Accepted** 15 August 2021 ♦ **Published** 24 September 2021

Citation: Galenko-Yaroshevsky PA, Nechepurenko AA, Pokrovskaya TG, Shimonovsky NL, Dukhanin AS, Suzdalev KF, Maslova PD, Makhnova NM, Shneivais VV, Abushkevich VG, Zelenskaya AV, Seletskaya VV, Ahedzhak-Naguse SK, Korotkov KG (2021) Role of indole derivative SS-68 in increasing the frequency range of cardiac rhythm control (reflex stimulation of the sinoatrial node). Research Results in Pharmacology 7(3): 73–81. https://doi.org/10.3897/rrpharmacology.7.75337

Abstract

Introduction: Cardiac pacing is indicated for sick sinus syndrome. It is performed with a pacemaker via electrodes implanted in the heart. This technique has several disadvantages. The search for alternative methods of cardiac pacing is underway. One of them is control of heart rhythm through stimulation of the tragus.

Objective: To perform the reflex stimulation of the sinoatrial node and to study the influence of the SS-68 substance on it.

Materials and methods: Two electrodes were fixed in the reflexogenic zone of rabbits' auricles, volleys of electrical impulses from an electrical stimulator were applied to the electrodes, and the synchronization range of volley frequency and cardiac contractions was recorded. This range was re-recorded again after injecting the SS-68 substance (2-phenyl-1-(3-pyrrolidine-1-cyclopropyl)-1H-indole hydrochloride) intravenously at a dose of 50 μg/kg. In other experiments on frogs in a high-frequency electromagnetic field, the process of excitation of the area of the medulla oblongata associated with the heart rhythm was visualized. After the application of SS-68 (50 μM) to the surface of this zone, the process of its excitation was recorded.

Results and discussion: Stimulation of the auricular reflexogenic zone of rabbits produced a synchronization of volley frequency and heart rate in the range from 173.5 ± 2.0 to 214.0 ± 1.8 per minute. SS-68 extended this range from 168.2 ± 1.9 to 219.4 ± 1.5 per minute. In the frog's medulla oblongata, an area synchronous to the heart rhythm glowed in the high-frequency electromagnetic field. SS-68 increased the area of glow by 131.0%.

Conclusion: The substance SS-68 increases the frequency range of heart rhythm control by activating reflex stimulation of the sinoatrial node. The main point of application of SS-68 is the medulla oblongata. Glow in the high-frequency electromagnetic field reflects the process of neuron excitation. The increase in the glow zone under the influence of SS-68 indicates synchronously excited neurons, which leads to the assimilation of the central heart rhythm generation by the sinoatrial node.

Keywords

SS-68 substance, visualization of excitation in the brain, reflex cardiostimulation.

Introduction

One of the problems of modern cardiology is cardiac pacing, which becomes necessary in case of sinus node dysfunction, or sick sinus syndrome, often resulting in alternating paroxysms of atrial fibrillation. The latter can be complicated by cardiogenic thromboembolism, stroke (Gardarsdottir et al. 2018; Nechepurenko et al. 2020), and sinus bradycardia – "brady-tachy syndrome" (Bektas and Soyuncu 2016; Brandt et al. 2017; Bougioukas et al. 2017; Jackson et al. 2017; Zhou et al. 2017). The generally accepted technique of cardiac pacing, along with the advantages, has several disadvantages, particularly, pacing ventricular premature beats, supraventricular tachycardia, endless loop tachycardia, and pacemaker syndrome in case of certain myocardial functional conditions, and the use of dual-chamber pacemaker. In addition, the widespread use of modern pacemakers in cardiology practice – dual-chamber, biventricular, frequency-adaptive, and anti-tachycardia – causes difficulties for attending physicians in interpreting electrocardiographic parameters and programming these devices when implanting them in patients with sick sinus syndrome. Although sick sinus syndrome is often a reason for installing a pacemaker, constant stimulation of the sinoatrial node in the corresponding category of patients does not continuously improve their survival rate, even though bradycardic manifestations are not detected (Revishvili et al. 2017).

Another way to stop cardiac rhythm disturbance in sick sinus syndrome is vagus nerve stimulation. Detection of volleys of electrical impulses in the efferent cardiac neurons of the medulla oblongata, synchronous with the heart rhythm, and in the efferent cardiac fibers of the vagus nerve prompted the development of the method of heart rhythm control by stimulation of the peripheral end of the cut vagus nerve by volleys of electrical impulses. As a result, the phenomenon of heart rhythm control was discovered, manifested by bradycardia, vagus-cardiac synchronization in a specific frequency range, and a paradoxical increase in the heart rhythm, when a higher frequency of volleys applied to the nerve, i.e. more intensive stimulation, causes a relative increase in the heart rhythm, rather than its fall (Pokrovsky 2007; Sitdikov et al. 2016).

Vagus-cardiac synchronization involves the application of a volley of electrical impulses to the peripheral end of the cut vagus nerve of the animal, which causes a cardiac contraction. Changing the frequency of volleys in a specific frequency range induces synchronous changes in the heart rate, which allows the control of the heart rhythm. However, due to the transection of the vagus nerve and irritation of all its fibers, this technique is not acceptable for humans.

To reduce the time of atrial fibrillation paroxysms in patients, percutaneous stimulation of the vagus nerve branch in the region of the tragus can be used (Syrovnev et al. 2017). This was confirmed by the marker of sympathetic nervous system activity – neuropeptide Y (Stavrakis et al. 2020a, 2020b).

The outer ear is the only place where the vagus nerve has its peripheral branch, which forms a cutaneous receptor field in the auricle. This field is receptive to external stimuli in terms of peripheral nerve stimulation; in particular, it provides easy external access through electrical stimulation of the auricular branch, and directly connects the applied stimuli to the brain stem. The latter mediates entry to higher brain regions through extensive projections to second- and third-order neurons in the brain. The auricle, especially its nerve endings, is a robust direct gateway for modulating various brain functions, offering the most accessible non-invasive manipulations of the central nervous system. The auricular branch leaves the cervical vagus nerve at the level of the jugular ganglion, where the sensory ganglion neurons have their bodies, just outside the skull. The endings of the auricular branch of the vagus nerve (ramus auricularis nervi vagi) provide sensory innervation of some regions of the outer ear. In addition to these, the ear contains the endings of non-vagal cervical and cranial nerves, such as the great auricular nerve – nervus auricularis magnus, located in the earlobe, the auriculotemporal nerve (a branch of the trigeminal nerve located in the spinal column), and the lesser occipital nerve – nervus occipitalis minor. Anatomically, all nerve fibers in the auricle lie between the auricular cartilage and the skin at a depth of 1–1.5 mm. Stimulation of the auricular branch of the vagus nerve engages the sensory fibers and thus projects the sensory input into the brainstem in terms of neuromodulation, forming the so-called auriculovagal afferent pathway.

Consequently, since the autonomic nervous system, consisting of sympathetic and parasympathetic branches, regulates the systemic parameters of cardiovascular, respiratory, and immunological functions to remain within their homeostatic limits, the auricular branch of the vagus nerve modulates the parasympathetic atrial branch, the effects of which may be of a systemic nature. Systemic effects affect several physiological functions and do not target a specific organ or isolated function. So, various physiological effects can be expected with stimulation of the auricular branch of the vagus nerve. Stimulation of this branch can be considered a peripheral, non-pharmacological, and least invasive neuromodulation method, changing the perception of signals in the central nervous system, activating reflex pathways, using brain plasticity for various therapeutic purposes, and, thus, affecting

a variety of brain areas. Functional magnetic resonance imaging has shown specific modulation of different brain structures, including its trunk and nuclei, the spinal nucleus of the trigeminal nerve, which are mainly connected with higher-order relays, afferent (visceral and somatic) pathways and networks, after stimulation of the auricular branch of the vagus nerve. However, the latter only produces a heart rhythm decrease (Kaniusas et al. 2019).

Objective of the study: to carry out reflex stimulation of the sinoatrial node and reveal the influence of SS-68 substance on it.

Materials and methods

Animals and experimental design

When conducting the experiments, the requirements of the Russian Federation Law "On the Protection of Animals From Cruel Treatment: of 24.06.1998, Rules of Laboratory Practice for Preclinical Studies in the Russian Federation (GOST 3 51000.3-96 and GOST R 53434-2009), the provisions of the Helsinki Declaration of the World Medical Association on the Humane Treatment of Laboratory Animals (Report of the AVMA Panel on Euthanasia JAVMA 2001), the European Society Directive (86/609 EC), the rules of International Recommendations of the European Convention for the Protection of Vertebrate Animals Used in Experimental Research (1997), and the rules of Laboratory Practice adopted in Russia (MHRP Order № 708 of 29.08.2010) were taken into account. Permission to perform the experiments was obtained from the Ethical Committee of Kuban State Medical University.

The first series of experiments was performed on non-narcotized 15 male chinchilla rabbits weighing 2.5–2.7 kg. The animals were fixed in a machine in a head-down position. An electrocardiogram in standard lead I was recorded on a computer cardiograph, and the initial heart rate was determined. Two-needle hook electrodes were fixed in the reflexogenic zone of the right auricle. The marked area was stimulated by volleys of 4 electric impulses of 2 ms duration and 80 Hz frequency by a universal electro stimulator (ESU-1, Russia) and an insulating block, after which synchronization of stimulation frequency and heart rate was determined in a specific frequency range of heart contractions per minute. After recording the initial synchronization parameters, the animals were injected intravenously (into the marginal vein of the left ear) with the SS-68 substance (hydrochloride 2-phenyl-1-(3-pyrrolidine-1-cyclopropyl)-1H-indole) synthesized in the Southern Federal University, Rostov-on-Don, in a dose of 50 μg/kg. In the control experiments, we used intravenous injection water in volumes equivalent to SS-68, 0.25% lidocaine solution (0.5 ml intradermally in the reflexogenic zone of the auricle), and sodium thiopental (40 mg/kg intraperitoneally).

The second series of experiments was performed on 30 lake frogs, *Rana ridibunda*, which were immobilized by destroying the spinal cord with a metal probe inserted into the spinal canal. The frogs were fixed with their abdomens downward. A trapezoidal skin incision was made on the head, and the cranium was opened. Above the medulla oblongata, the scanner of the KELSI device (ELSIS, St. Petersburg) was placed over the frog's medulla, creating a high-frequency electric field (1024 Hz). A 64-second video film was shot with a scanner TV camera, during which the area of luminescence in the area of the medulla oblongata associated with the heart rhythm was visualized. The flow-chart of the setup is shown in Fig. 1.

Figure 1. Flow-chart of the setup for registration of the glow focus in the frog medulla. **Note:** 1 – KELSI device; 2 – electrode for electrocardiogram; 3 – KELSI control unit; 4 – monitor; 5 – frog medulla; 6 – computer electrocardiograph.

The video film was divided into frames by a computer program, in which the areas of luminescence zones of different brightness and wavelengths were determined. After recording the areas of luminescence in the initial state, SS-68 (50 μM) was applied to the surface of the medulla oblongata, and the area of luminescence was recorded again 15 minutes later. Injection water in volumes equivalent to those of SS-68 was used as a control.

Statistical analysis

A statistical analysis of the results was performed using STATISTICA 10 software, using Student's t-test. The difference between the mean values was considered reliable at $p < 0.05$.

Results and discussion

The initial heart rate in rabbits was 201.2 ± 3.3 per minute. When the reflexogenic zone of the auricle was stimulated with volleys of electrical impulses in the frequency

range of 173.5 ± 2.0 to 214.0 ± 1.8 of heart contractions per minute, synchronization of stimulation frequency and heart contractions was observed. For each volley of impulses applied to the reflexogenic zone, the heart responded with one contraction. Variation of stimulation frequency led to the synchronous change of heart contractions, thus creating an opportunity to control the heart rhythm.

In the control studies, moving the stimulating electrodes outside the reflexogenic zone of the auricle resulted in the disappearance of synchronization. The latter also disappeared during infiltration of the skin of the reflexogenic zone with lidocaine. In addition, the range of synchronization sharply decreased in anesthetized (with thiopental sodium) animals. These facts indicate the reflexogenic nature of synchronization.

Intravenous administration of SS-68 resulted in a widening of the synchronization range, from 168.2 ± 1.9 to 219.4 ± 1.5 heartbeats per minute, whereas in the control studies, injected water did not cause this phenomenon.

Since the synchronization effect in the experiments on rabbits was reflexive, and SS-68 substance increased the synchronization range of stimulation frequency of the auricular reflexogenic zone and heart contractions, the experiments were performed on frogs to visualize neural activity in the areas of the medulla oblongata, the activity of which is associated with the heart rhythm (Fig. 2).

The focus of glow periodically appeared and disappeared before the V wave, which reflected the excitation of the venous sinus. Such dynamics served as a basis for the assumption that the glow focus in the frog's medulla oblongata reflected excitation of the cardiovascular center. The observed focus of luminescence included zones of the most intensive and less intensive luminescence (Figs 2, 3).

Table 1. Luminescence Areas in the Frog's Medulla Oblongata Before and After SS-68 Application (M ± m, n = 30)

Glow zones	Dimensions of the areas of the glow zones in mm²	
	Before SS-68 application	After SS-68 application
1 zone	0.29 ± 0.05	0.670 ± 0.002
		$p < 0.001$
2 zone	0.36 ± 0.04	0.220 ± 0.002
		$p < 0.001$
3 zone	0.14 ± 0.01	0.120 ± 0.001
		$p > 0.05$
4 zone	0.15 ± 0.2	0.070 ± 0.001
		$p < 0.001$
5 zone	0.11 ± 0.04	0.040 ± 0.001
		$p < 0.001$
6 zone	0.10 ± 0.02	0.080 ± 0.001
		$p > 0.05$
7 zone	0.15 ± 0.02	0.100 ± 0.001
		$p < 0.001$

The dynamics of the luminescence area on the scanogram before and after SS-68 injection is shown in Figures 4, 5, and the Table 1.

After applying SS-68, the 1st zone of the glow area increased by 131.0%, and the glow areas of the 2nd, 3rd, 4th, 5th, 6th, and 7th zones decreased by 38.9, 14.3, 53.3, 63.6, 20.0, and 33.3%, respectively.

Since the control of the heart rhythm occurred in a reflex way, and the SS-68 substance increased this effect, the point of application of this substance is the medulla oblongata. It had been previously shown that the glow in the high-frequency electromagnetic field reflects the process of neuronal excitation (Bogus et al. 2018). Consequently, the observed expansion of the area of the 1st zone of the glow focus under the influence of SS-68 indicates an increase in the synchronously excited neuronal networks.

The study of brain rhythms and synchronization of oscillatory activity is currently one of the most discussed

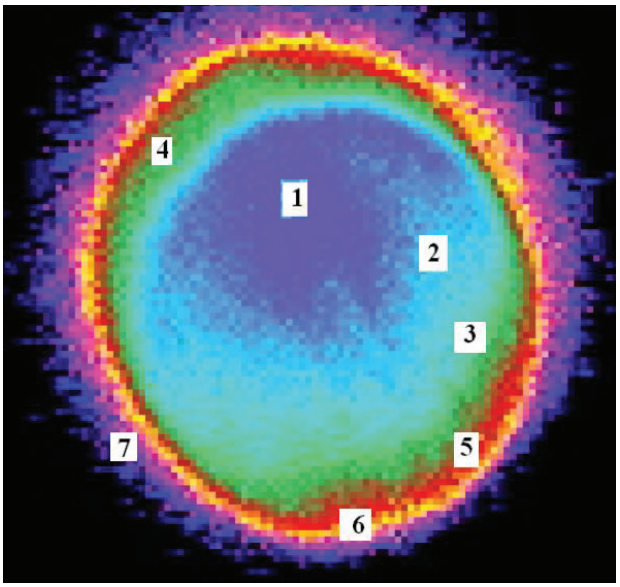

Figure 2. The luminescent focus in the frog medulla in a high-frequency electromagnetic field before SS-68 application. **Note:** 1 – zone of the most intensive glow; 2–7 – zones of less intensive glow.

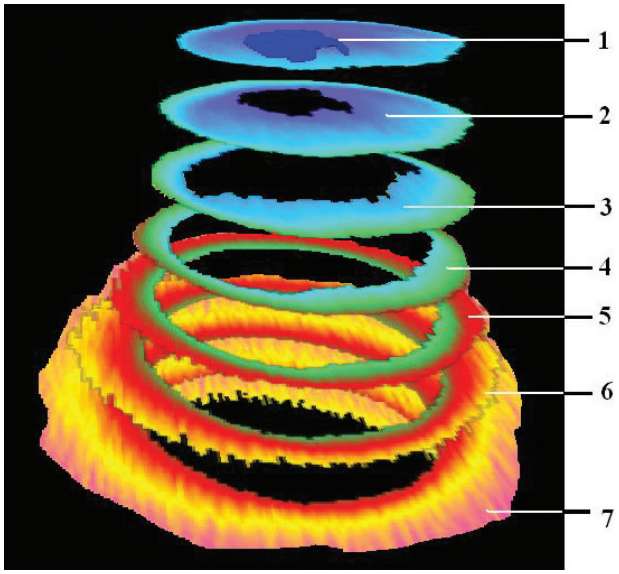

Figure 3. Fragments of the luminescent focus in the frog's medulla oblongata in a high-frequency electromagnetic field before SS-68 application. **Note:** 1 – zone of the most intensive glow; 2–7 – zones of less intensive glow.

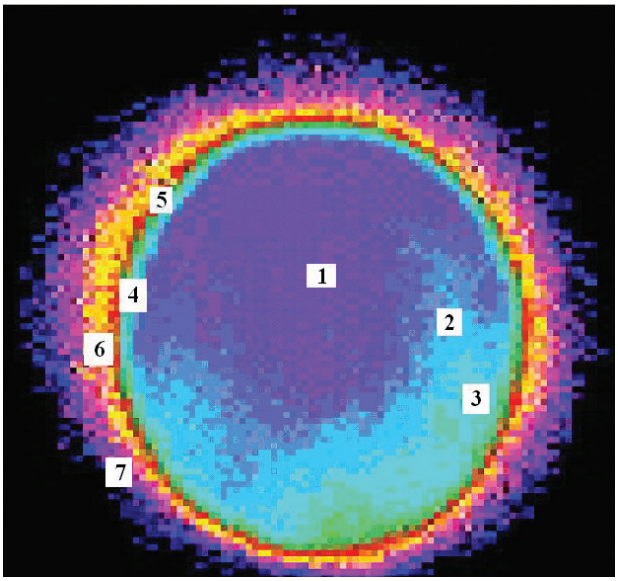

Figure 4. Luminescent focus in the frog's medulla oblongata in a high-frequency electromagnetic field after application of SS-68. **Note:** 1 – zone of the most intensive glow; 2–7 – zones of less intensive glow.

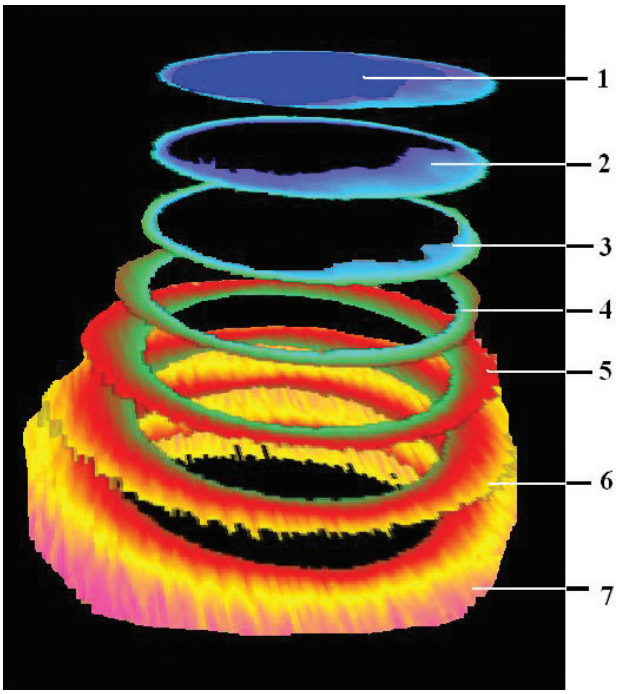

Figure 5. Fragments of the luminescent focus in the frog's medulla oblongata in a high-frequency electromagnetic field after application of SS-68. **Note:** 1 – zone of the most intensive glow; 2–7 – zones of less intensive glow.

topics in neurobiology. Experimental studies of brain rhythms and neuronal synchronization have been accompanied by intensive efforts to understand rhythm generation and mechanisms of neuronal synchronization using computer modeling and nonlinear dynamics.

The oscillatory activity of the central nervous system manifests itself at different spatial and temporal scales, including spike sequences, local field potentials, and large-scale oscillations. Individual neurons exhibiting rhythmic pulse or burst activity can often be considered self-sustaining oscillators (Ermentrout and Terman 2010).

The term "neural synchronization" is widely used in the neurobiology literature. In its most common meaning, it refers to the temporal correlation between brain signals. It is an operational and statistical definition based on how synchrony between brain signals is measured. For this reason, neurogenic synchronization depends on scale and space.

At the cellular level, synchronization is measured by cross-correlograms of spike chains, usually correlating with local field potential fluctuations. The implication is that neurons are synchronized if they burst at the same time. On the other hand, the physical definition of synchronization is more general, given the possibility of a phase shift between synchronized signals.

Synchrony can also be measured between spatially separated brain regions – the so-called large-scale neuronal synchronization, which in principle is phase synchronization (measuring phase correlation, but not amplitude correlation).

Synchronization as "endogenous neural oscillations" in neurobiology represents rhythmic oscillations in the excitation-inhibition cycle of neuronal populations.

We may be based on V.M. Pokrovsky's concept of cardiac rhythm initiation in the central nervous system (Pokrovskii 2003, 2005, 2006; Pokrovsky 2007; Pokrovskii and Polischuk 2016), particularly in the medulla oblongata, in the form of volleys of nerve impulses that reach the sinoatrial node via vagus nerves and are digested there. In that case, SS-68 seems to enhance the process of central generation of the heart rhythm.

Serotonin (5-hydroxytryptamine - 5 NT) is one of the phylogenetically older molecules used in cell communication. It is present in the central nervous system and plays the role of a neurotransmitter/neuromodulator. In the brain, the serotoninergic system is involved in many functions due to its wide distribution in the neuraxis. Axons of serotonergic neurons of the midbrain suture nuclei reach almost all the brain structures. Action potentials travel along these axons to release 5-NT, which can act on pre- and post-synaptic receptors associated with various signal transduction mechanisms. To date, 14 different subtypes of 5-HT receptors have been identified, corresponding to 7 different families. Except for the 5-HT3 receptor and the pentameric ion channel, the remaining 5-HT receptors belong to the G-protein-coupled receptor superfamily. Their activation leads mainly to modulatory effects in neurons expressing these receptors (Celada et al. 2013).

Given the richness of 5-HT-induced signals, it is not surprising that the serotonin system is the target of action of many drugs.

Among the various 5-HT receptors, the 5-HT1 family has probably attracted the most attention because of its high expression density in limbic (5-HT1A) and motor (5-HT1B) brain regions and their various functions. In addition to their post-synaptic localization, 5-HT1A and

5-HT1B receptors are autoreceptors in serotonergic neurons and therefore control overall (5-HT1A) and local (5-HT1B) activities of the system. 5-HT1B receptors are also terminal heteroreceptors and modulate the release of various transmitters, including dopamine, glutamate, GABA, and acetylcholine. Moreover, 5-HT1A receptors are highly expressed by different types of neurons, mainly pyramidal, and GABAergic in the prefrontal cortex (Artigas 2013). These facts indicate the involvement of various kinds of receptors belonging to different families of membrane receptors, the neurotransmitters of the central nervous system.

Steriade (2006) described in detail the involvement of 5-HT in the modulation of cellular mechanisms underlying spontaneous slow rhythms of neurons. Slow waves reflect unexpected changes in membrane potential and synchronous activation of ensembles of neurons coordinated by underlying slow oscillations. They reflect periods of membrane depolarization and hyperpolarization at the cellular level, respectively, within large neuronal networks (Mukovski et al. 2007). 5-HT appears to have an excitatory effect on cortical networks due to synchronous depolarization of large ensembles of cortical structures. Balanced stimulation of 5-HT2A receptors is crucial for stable synchronization of slow cortical waves.

Along with slow waves, fast waves (gamma oscillations) are present in the cortex (Massi et al. 2012). The synchronous triggering of interneuron networks generates gamma oscillations. 5-HT1A receptors exacerbate the synchronization of interneurons with gamma cycles. In contrast, blocking 5-HT2A receptors reduces cortical gamma oscillations and desynchronizes 5-HT2A-expressing interneurons. Endogenous 5-HT can attenuate or enhance gamma oscillations, decreasing or increasing activity and synchronization of expressing 5-HT1A and 5-HT2A interneurons.

According to our earlier studies, SS-68 (50 μM) in the experiments on synaptosomes obtained from the ventrolateral surface of the cat medulla oblongata does not affect the functional activity of 5-NT3, GABA and NMDA receptor types conjugated to ion channels (1st and 3rd receptors to calcium channels, 2nd receptors to chloride ionophores), and acts antagonistically on NMDA receptors connected to sodium channels. The SS-68 substance shows no significant effect on 5-HT1, 5-HT2, and Met-Glu receptors associated with G-proteins, whereas it has a marked blocking effect on β-adrenoreceptors. These data indicate the involvement of two types of receptors (NMDA and β-adrenoreceptors) representing different families of these membrane structures of the central nervous system in the implementation of the neurotropic action of SS-68. At the same time, it is difficult to believe that the observed effects of SS-68 are related to its direct impact on the receptors. It is possible that SS-68, while not showing direct affinity to NMDA glutamate receptors and various types of serotonin receptors, can have a modifying/allosteric effect on them by activating or inhibiting their ability to enhance or weaken the molecular signal to the transducer or effector (Bogus et al. 2012).

SS-68 can arrest cardiac rhythm disturbances of central genesis: when administered intravenously in a wide range of doses against the background of intracisternal (into the fourth ventricle of the brain) injections of aconitine (disrupts sodium channels), strophanthin K (inhibits membrane Na+K+-ATPase, and thus changes neurotransmitter activity) and cesium chloride (blocks transmembrane potassium channels) in microdoses of 2–6 μg/kg, 0. 01–0.05 and 0.5–1.5 mg/kg in cats (Bogus et al. 2018), and micro application of SS-68 to cortical neurons in the right and left regions of rat somatosensory cortex eliminates the arrhythmogenic effects of the M- and H-cholinomimetic carbachol (12.5 mM). This fact is noteworthy because it sheds light on some features and mechanisms of SS-68 action on the functional organization of brain cholinergic neurons. In particular, the cholinergic regulation of heart rhythm by the vagus nerve, the nuclei of which are located in the medulla oblongata, is well known. Somewhat higher up in the brain stem, the primary nuclei of the cholinergic neurons regulating rhythmogenesis of the hippocampus and the new cortex are located. In the cortex itself, only some of the neurons respond with excitation to direct application of acetylcholine. It is conceivable that SS-68 also acts on these neurons, which are included in the pathways of cholinergic influences along the corticobulbar pathways to the nuclei of the vagus nerves containing cholinergic neurons, which explains the facts of changes in the heart rhythm. It is possible that the changes in the heart rhythmic activity under the influence of SS-68 are related to its action on various microsystems of neuronal populations of different mediator affiliation, the sequential activation of which in different combinations is carried out following the genetic programs of maintaining the standard resting potential of individual neurons and the homeostasis of the brain activity as a whole.

Moreover, it was found that in experiments on isolated unidentified neurons of the great pond snail (*Lymnae stagnalis*) and ramshorn snail (*Planorbarius corneus*), SS-68 at concentrations of 1 and 10 μM induced activation of sodium and potassium slow currents, accelerated inactivation of potassium currents and slightly pronounced hyperpolarization of these neurons. With an increase in the SS-68 concentration up to 100 and 1000 μM, blocking off the marked ionic currents was observed (Vislobokov et al. 2012). In the experiments on rat hippocampal neuron culture, SS-68 at concentrations of 1.3 and 5 μM inhibited delayed rectifier potassium currents and, as a consequence, caused prolongation of the action potential and reduction of its impulse generation (Zinchenko et al. 2013).

Based on the current concepts of new-type biologically active substances that are not direct agonists of receptor structures, the molecular mechanism of action of SS-68 on reflex stimulation of the sinoatrial node can be

represented as the effect of a modulator that allosterically potentiates the receptor-ligand and activates various ion channels or as the result of new binding options of endogenous ligands to the most optimal receptor subtypes that model the secondary intracellular mediators under the influence of SS-68.

Conclusion

The SS-68 substance increases the frequency range of heart rhythm control by activating reflex stimulation of the sinoatrial node. The main point of application of SS-68 is the medulla oblongata. Glow in the high-frequency electromagnetic field reflects the process of neuron excitation. The increase in the glow zone under the influence of SS-68 indicates synchronously excited neurons, which leads to the assimilation of the central heart rhythm generation by the sinoatrial node.

SS-68 exhibits the multitarget action against central neurochemical structures that may be involved in the regulation of heart rhythm. Apparently, under the influence of SS-68, conformational changes take place in the membrane receptors of neurotransmitters,, conjugated with ion channels in the medulla oblongata and other parts of the central nervous system, in particular, in the cerebral cortex and hippocampus. The activation of the central heart rhythm regulation by SS-68 is also possible due to new variants of binding the endogenous ligands to the most optimal receptor subtypes, improvement of conjugation of membrane receptors, and G-proteins, which affects receptor structures that change the system of secondary intracellular mediators.

Conflict of interests

The authors declare that there is no conflict of interests.

References

- Artigas F (2013) Serotonin receptors involved in antidepressant effects. Pharmacology & Therapeutics 137(1): 119–131. https://doi.org/10.1016/j.pharmthera.2012.09.006 [PubMed]
- Bektas F, Soyuncu S (2016) The efficacy of transcutaneous cardiac pacing in ED. The American Journal of Emergency Medicine 34(11): 2090–2093. https://doi.org/10.1016/j.ajem.2016.07.022 [PubMed]
- Bogus SK, Galenko-Yaroshevsky PA, Dukhanin AS, Shimanovsky NL (2012) Comparative study of the effects of the SS-68 indole derivative, amidorone and dronedarone on the functional activity of different types of receptors on the ventrolateral surface of the medulla oblongata. New Technologies [Novye Tekhnologii] 4: 239–247. [in Russian]
- Bogus SK, Galenko-Yaroshevsky PA, Suzdalev KF, Sukoyan GV, Abushkevich VG (2018) 2-phenyl-1-(3-pyrrolidin-1-il-propyl)-1H-indole hydrochloride (SS-68): antiarrhythmic and cardioprotective activity and Its molecular mechanisms of action (Part I). Research Results in Pharmacology 4(2): 133–150. https://doi.org/10.3897/rrpharmacology.4.28592
- Bougioukas I, Jebran AF, Grossmann M, Friedrich M, Tirilomis T, Schoendube FA, Danner BC (2017) Is there a correlation between late reexploration after cardiac surgery and removal of epicardial pacemaker wires. Journal of Cardiothoracic Surgery 12(1): e3. https://doi.org/10.1186/s13019-017-0569-5 [PubMed] [PMC]
- Brandt NH, Kirkfeldt RE, Nielsen JC, Mortensen LS, Jensen GVH, Johansen JB, Haugan K (2017) Single lead atrial vs. dual chamber pacing in sick sinus syndrome: extended register-based follow-up in the DANPACE trial. Europace 19(12): 1981–1987. https://doi.org/10.1093/europace/euw364 [PubMed]
- Celada P, Puig MV, Artigas F (2013) Serotonin modulation of cortical neurons and networks. Frontiers in Integrative Neuroscience 7: e25. https://doi.org/10.3389/fnint.2013.00025 [PubMed] [PMC]
- Ermentrout GB, Terman DH (2010) Mathematical Foundations of Neuroscience. Springer-Verlag, New York, 422 pp. https://doi.org/10.1007/978-0-387-87708-2
- Gardarsdottir M, Sigurdsson S, Aspelund T, Rokita H, Launer LJ, Gudnason V, Arnar DO (2018) Atrial fibrillation is associated with decreased total cerebral blood flow and brain perfusion. Europace 20(8): 1252–1258. https://doi.org/10.1093/europace/eux220 [PubMed] [PMC]
- Jackson II LR, Rathakrishnan B, Campbell K, Thomas KL, Piccini JP, Bahnson T, Stiber JA, Daubert JP (2017) Sinus node dysfunction and atrial fibrillation: a reversible phenomenon. Pacing and Clinical Electrophysiology 40(4): 442–450. https://doi.org/10.1111/pace.13030 [PubMed]
- Kaniusas E, Kampusch S, Tittgemeyer M, Panetsos F, Gines RF, Papa M, Kiss A, Podesser B, Cassara AM, Tanghe E, Samoudi AM, Tarnaud T, Joseph W, Marozas V, Lukosevicius A, Ištuk N, Šarolić A, Lechner S, Klonowski W, Varoneckas G, Széles JC (2019) Current directions in the auricular vagus nerve stimulation I – a physiological perspective. Frontiers Neuroscience 13: e854. https://doi.org/10.3389/fnins.2019.00854 [PubMed] [PMC]
- Massi L, Lagler M, Hartwich K, Borhegyi Z, Somogyi P, Klausberger T (2012) Temporal dynamics of parvalbumin-expressing axo-axonic and basket cells in the rat medial prefrontal cortex in vivo. Journal of Neuroscience 32(46): 16496–16502. https://doi.org/10.1523/JNEUROSCI.3475-12.2012 [PubMed] [PMC]
- Mukovski M, Chauvette S, Timofeev I, Volgushev M (2007) Detection of active and silent states in neocortical neurons from the field potential signal during slow-wave sleep. Cerebral Cortex 17(2): 400–414. https://doi.org/10.1093/cercor/bhj157 [PubMed]
- Nechepurenko AA, Pokrovsky VM, Tarasov DG, Kitiashvili IZ, Abushkevich VG (2020) Cardiac uptake of vagus nerve rhythm in patients with paroxysmal atrial fibrillation. General Resuscitation 16(3): 46–53. https://doi.org/10.15360/1813-9779-2020-3-46-53 [in Russian]

- Pokrovskii VM (2003) Alternative view on the mechanism of cardiac rhythmogenesis. Heart Lung Circulation 12(1): 18–24. https://doi.org/10.1046/j.1444-2892.2003.00192.x [PubMed]
- Pokrovskii VM (2005) Integration of the heart rhythmogenesis levels: heart rhythm generator in the brain. Journal of Integrative Neuroscience 4(2): 161–168. https://doi.org/10.1142/S0219635205000793 [PubMed]
- Pokrovskii VM (2006) Hierarchy of the heart rhythmogenesis levels is a factor in increasing the reliability of cardiac activity. Medical Hypotheses 66(1): 158–164. https://doi.org/10.1016/j.mehy.2005.06.028 [PubMed]
- Pokrovskii VM, Polischuk LV (2016) Cardiorespiratory synchronism in estimation of regulatory and adaptive organism status. Journal of Integrative Neuroscience 15(1): 19–35. https://doi.org/10.1142/S0219635216500060 [PubMed]
- Pokrovsky VM (2007) Formation of heart rhythm in human and animal organisms. Krasnodar, 14 pp. [in Russian]
- Revishvili ASH, Bayramova SA, Boytsov SA, Davtyan KV, Egorov DF, Zenin SA, Kalemberg AA, Krivolapov SN, Kuznetsov VA, Kuptsov BB, Lebedev DS, Lomidze NN, Neminushchiy NM, Pokushalov EA, Popov SV, Serdyuk SE, Simonyan GY, Tarasov AV, Chugunov IA, Chudinov GV (2017) Clinical recommendations for the use of pacemakers, implantable cardioverter-defibrillators, cardiac resynchronization therapy devices and implantable cardiac monitors. In: Clinical Guidelines for Electrophysiology, Catheter Ablation and the Use of Implantable Antiarrhythmic Devices. Moscow, 13–212. [in Russian]
- Sitdikov FG, Gizzatullin AR, Ziyatdinova NI (2016) Vagus regulation of the developing heart. Kazan (Volga Region) Federal University, Kazan, 234 pp. [in Russian]
- Stavrakis S, Morris L, Takashima AD, Elkholey K, van Wagoner DR, Ajijola OA (2020a) Circulating neuropeptide Y as a biomarker for neuromodulation in atrial fibrillation. JACC: Clinical Electrophysiology 6(12): 1575–1576. https://doi.org/10.1016/j.jacep.2020.08.025 [PubMed]
- Stavrakis S, Stoner JA, Humphrey MB, Morris L, Filiberti A, Reynolds JC, Elkholey K, Javed I, Twidale N, Riha P, Varahan S, Scherlag BJ, Jackman WM, Dasari TW, Po SS (2020b) TREAT AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation): a randomized clinical trial. JACC: Clinical Electrophysiology 6(3): 282–291. https://doi.org/10.1016/j.jacep.2019.11.008 [PubMed] [PMC]
- Steriade M (2006) Grouping of brain rhythms in corticothalamic systems. Neuroscience 137(4): 1087–1106. https://doi.org/10.1016/j.neuroscience.2005.10.029 [PubMed]
- Syrovnev VA, Lebedev DS, Mikhailov EN (2017) Vagus nerve stimulation in cardiology. Translational Medicine 4(2): 6–16. https://doi.org/10.18705/2311-4495-2017-4-2-6-16 [in Russian]
- Vislobokov AI, Bogus SK, Ignatov JD, Galenko-Yaroshevsky PA, Melnikov KN (2012) Comparative membranotropic activity of indole derivative SS-68 and aminodaron on mollusc neurons. New Technologies [Novye Tekhnologii] 4: 283–290. [in Russian]
- Zhou Y, Lower EE, Li HP, Costea A, Attari M, Baughman RP (2017) Cardiac sarcoidosis: the impact of age and implanted devices on survival. Chest Journal 151(1): 139–148. https://doi.org/10.1016/j.chest.2016.08.1457 [PubMed]
- Zinchenko VP, Kononov AV, Berezhnov AV, Teplov IV, Bogus SK (2013) Mechanism of action of antiarrhythmic SS-68. V. Yema Publishing House LLC, Moscow, 442–447. [in Russian]

Author contributions

- **Pavel A. Galenko-Yaroshevsky,** Corresponding member of the Russian Academy of Sciences, Dr. habil. of Medical Sciences, Professor, Head of the Department of Pharmacology, Kuban State Medical University, Krasnodar, Russia, e-mail: Galenko.Yarochevsky@gmail.com, **ORCID ID** http://orcid.org/0000-0001-6856-1777. The author made a significant contribution to the concept of the effect of the SS-68 substance on cardiac rhythmogenesis.

- **Anatoly A, Nechepurenko,** MD, PhD, Head of the Department of Surgical Arrhythmology, Federal Center for Cardiovascular Surgery, Astrakhan, Russia, e-mail: vestik@mail.ru, **ORCID ID** http://orcid.org/0000-0001-5722-9883. The author made a significant contribution to the concept of mechanisms of reflex control of heart rhythm.

- **Tatiana G. Pokrovskaya,** Dr. habil. of Medical Sciences, Professor of the Department of Pharmacology and Clinical Pharmacology of the Institute of Medicine, head of the Clinical Research Laboratory of the Research Institute of Pharmacology of Living Systems of Belgorod State University, Belgorod, Russia, e-mail: tpokrovsky@yandex.ru, **ORCID ID** http://orcid.org/0000-0001-6802-5368. The author made a significant contribution to the concept of the effect of SS-68 on cardiac rhythmogenesis.

- **Nikolay L. Shimanovsky,** Corresponding Member of the Russian Academy of Sciences, Dr. habil. of Medical Sciences, Professor, Head of the Department of Molecular Pharmacology and Radiobiology, Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: shimannn@yandex.ru, **ORCID ID** http://orcid.org/0000-0001-5722-9883. The author analyzed and interpreted the results of the study.

- **Alexander S. Dukhanin,** Dr. habil. of Medical Sciences, Professor, Department of Molecular Pharmacology and Radiobiology, Pirogov Russian National Research Medical University, Moscow, Russia, e-mail: das03@rambler.ru, **ORCID ID** http://orcid.org/0000-0001-5722-9883. The author analyzed and interpreted the results of the study.

- **Konstantin F. Suzdalev,** PhD in Chemical Sciences, Associate Professor, Department of Chemistry of Natural and High-Molecular Compounds, Southern Federal University, Rostov-on-Don, Russia, e-mail: konsuz@gmail.com, **ORCID ID** http://orcid.org/0000-0002-6818-084. The author performed the synthesis of the SS-68 substance and made a significant contribution to the concept of its effect on cardiac rhythmogenesis.

- **Polina D. Maslova,** assistant of the Department of Nervous Diseases and Neurosurgery with a course of nervous diseases and neurosurgery of the Faculty of Pedagogical Problems of Kuban State Medical University, Krasnodar, Russia, e-mail: polinamaslova@mail.ru. The author participated in obtaining reflex control of heart rhythm in rabbits.

- **Natalia M. Makhnova,** postgraduate student, Department of Normal Physiology, Kuban State Medical University, Krasnodar, Russia, e-mail: agapinata6a1@mail.ru. The author participated in collection of material on visualization of luminescence (excitation) in areas of medulla oblongata.

- **Vadim V.Sheivais,** postgraduate student, Department of Normal Physiology, Kuban State Medical University, Krasnodar, Russia. e-mail: shneyways@yandex.ru. The author participated in obtaining reflex control of heart rhythm in rabbits.

- **Valery G. Abushkevich,** Dr. habil. of Medical Sciences, Professor, Chair of the Department of Normal Physiology, Kuban State Medical University, Krasnodar, Russia, e-mail: Abushkevich_v@mail.ru, **ORCID ID** http://orcid.org/0000-0002-1483-0131. The author performed an analysis and interpretation of the study results.

- **Anait V. Zelenskaya,** M.D., PhD, Associate Professor, Department of Pharmacology, Kuban State Medical University, Krasnodar, Russia, e-mail: anait_06@mail.ru, **ORCID ID** http://orcid.org/0000-0001-9512-2526. The author participated in the processing of the obtained data.

- **Valeria V. Seletskaya,** M.D., PhD, assistant of the Department of Pharmacology, Kuban State Medical University, Krasnodar, Russia, e-mail: seleckaya.v@mail.ru, **ORCID ID** http://orcid.org/0000-0002-0007-1971. The author participated in the processing of the obtained data.

- **Saida K. Akhedzhak-Naguse,** PhD, Assistant Professor of the Department of Public Health, Healthcare and History of Medicine, Kuban State Medical University, Krasnodar, Russia, e-mail: naguzesk@mail.ru, **ORCID ID** http://orcid.org/0000-0002-1573-9970. The author participated in the processing of the data obtained.

- **Konstantin G. Korotkov,** PhD, Professor, Lead Researcher of St. Petersburg Research Institute of Physical Culture, St. Petersburg, Russia. e-mail: korotkov2000@gmail.com, **ORCID ID** http://orcid.org/0000-0001-9043-1012. The author participated in the creation of the excitation visualization setup.