



On mechanism of antiarrhythmic action of some dimethylphenylacetamide derivatives

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Abstract

Abbreviations: AC – acetylcholine; AF – atrial fibrillation; AP – action potential; BLM – bi-lipid membrane; DPA – Dimethylphenylacetamide; VA – ventricular arrhythmia

Introduction: The *study aim* was to identify essential elements of the antiarrhythmic action mechanism of tertiary and quaternary derivatives of Dimethylphenylacetamide.

Materials and Methods: The study was conducted in albino rats and mice of both sexes; isolated neurons of mollusc *Limnaea stagnalis*; and strips of rats' right ventricle myocardium. Two compounds of Dimethylphenylacetamide LKhT-3-00 and LKhT-12-02 were studied. The cholynolytic property of the compounds was investigated by using a Schallek method in the authors' modification. The adrenotropic activity of the derivatives was explored by Moore et al. (1984), as well as by the method of catecholamine level detection in heart tissue. The permeability of derivatives through BLM was evaluated experimentally and theoretically. The derivatives' influence on Na⁺-current was studied directly and indirectly.

Results and Discussion: Neither tertiary nor quaternary derivatives possess the cholynolytic property. LKhT-3-00 prevented an increase in the adrenaline concentration in the left ventricle myocardium. The compounds prevent catecholamine arrhythmia and conductivity disorders. LKhT-3-00 like Lidocaine passes through the BLM of the cardiac cell in an ionised form, whereas the quaternary derivative permeates cardiac cell membrane in an electro-neutral form. Lidocaine derivatives restrain acute ischemia-induced oxidative process growth in the cardiac muscle. Simultaneously, the LKhT-3-00 compound can activate antioxidant mechanisms and prevent acidosis and optimise the balance between [O₂] and [CO₂] concentrations in coronary dark blood. At a concentration of 10 mg/ml, although the derivatives reduce the amplitude of the leading edge of AP and its rate of increase, they do not, however, affect the duration of AP.

Conclusions: The compounds possess the Na⁺-blocking and cell-protecting properties. They do not affect K⁺-current through Kv4.3-channels.

Keywords

antiarrhythmic activity, Dimethylphenylacetamide derivatives, tertiary and quaternary compounds, mechanism of action, action potential, permeability, arrhythmia, catecholamine

Introduction

Antiarrhythmic drugs have been in use for over 100 years to prevent and treat heart rhythm disorder despite many limitations and adverse effects (Castro et al. 2015). Their role of being the essential part of antiarrhythmic therapy inspires researchers to create novel molecules all over the world.

The mechanism of action is the cornerstone, which determines the therapeutic effectiveness and safety profile of an antiarrhythmic drug. It might be defined as an assembly of functional transformations of intracellular homeostasis and extracellular interaction that ultimately determines the pharmacological property of a drug.

In the early 2000s in Russia, a few novel molecules, DPA (Lidocaine) derivatives, were synthesised (Sernov et al. 2005). The main reason for developing the substances was the short duration of Lidocaine therapeutic activity, which makes it impossible to administer the drug orally for prophylaxis (Collinsworth et al. 1974).

Lidocaine chemical modification was conducted in two ways. The simplest and less expensive one resulted in producing tertiary DPA derivatives. Having their base unchanged, they had the anionic part of their molecule modified from nonorganic to amino acid or carbonic acid-containing fragments (Blinov et al. 2004). The more complicated way of chemical modification was a more complex synthesis, conducted on the basis of computer prognosis of structure-toxicity and structure-activity (Blinov et al. 2014).

The substances, representatives of both methods of chemical modification, have been experimentally studied for many years at The All-Russia Research Centre For Safety of Biologically Active Compounds (Sernov et al. 2005), Ogarev Mordovia State University (Blinov et al. 2004, Blinov et al. 2014, Blinova et al. 2015) and Tver State Medical University (Marasanov et al. 2013A, Marasanov et al. 2013b).

The studies showed that modification of the DPA molecule anion fragment leads to a decrease in acute toxicity of the novel substance when administering *parenterally and, maintaining* the initial antiarrhythmic level of Lidocaine activity, the duration of the pharmacological effect increases (Blinov et al. 2014). In particular, such conclusions were made when studying the derivatives containing remains of L-Glutamic, N-Acetyl-L-Glutamic and Succinic acid as anion fragments of the molecules (Blinov et al. 2004), whereas some substances, particularly those with the remains of L-Arginine, Acetylcysteine and Glycine as anionic groups demonstrated no substantial effect when compared with the structural analogue. Moreover, they would lose their antiarrhythmic property. In addition, it should be emphasised that an increased effect duration is accompanied by the molecule haemodynamic profile optimisation (Balashov et al. 2005).

Quaternary DPA derivatives were produced by targeting the nitrogen of the aliphatic fragment of the molecule by analogy with developing a national antiarrhythmic

drug quaternin, which is a quaternary allylmorpholinic derivative of Trimethylphenylacetamide (Balashov et al. 2005). The new substance appeared to be more active than Lidocaine and possessed a promising antiarrhythmic effect. However, one of the weak points of the compound was its higher toxicity in comparison with the structural ancestor.

Though, along with studying the effects of the compounds, different opinions about possible mechanisms of the derivative therapeutic action have been expressed, no complete and logically structured study has ever been conducted, which ultimately filled the authors with determination to conduct the current study.

The study aim was to identify the essential mechanism of antiarrhythmic action of tertiary - containing L-Glutamic acid remains - and quaternary allylmorpholinic DPA derivatives.

Materials and Methods

The protocols of the laboratory experiments included in the study underwent an ethical review at a meeting of the Local Ethical Committee of the Medical Institute of Ogarev Mordovia State University (minutes №5 of 22 October 2003).

Animals and Biological Materials

Experiments were made in 84 albino male and female rats with an average weight 193.0 ± 4.2 g, 112 albino mice of both sexes with average weight 18.4 ± 1.5 g, 60 papillary muscular strips isolated from albino rats' right ventricles and 12 gigantic neurons of mollusc *Limnaea stagnalis* parapharyngeal ganglion. The animals and biological material were purchased at the "Stolbovaya" and "Electrogorskiy" Departments of The Russian Research Centre for Biological Technologies and The Institute of Cell Biophysics of The Russian Academy of Sciences and maintained under required conditions at the University Novel Medication Research Centre. In case of invasive manipulation, all animals were obligatorily anaesthetised with either Ether inhalation or by *iv* administration of Urethane or Thiopental-sodium.

Substances and Drugs

Two novel pharmacologic substances, developed at The All-Russian Research Centre for Safety of Biologically Active Compounds (Sernov et al. 2005) and Ogarev Mordovia State University (Blinov et al. 2014), were investigated (Fig. 1 contains chemical structures of the substances) in the form of fine white water-soluble powder without or with insignificant odour. To validate the pharmacologic methods used in the laboratory and to compare the obtained results with those for the references, some reference drugs were used, above all the chemical precursor of lidocaine - hydrochloride. When modelling ace-

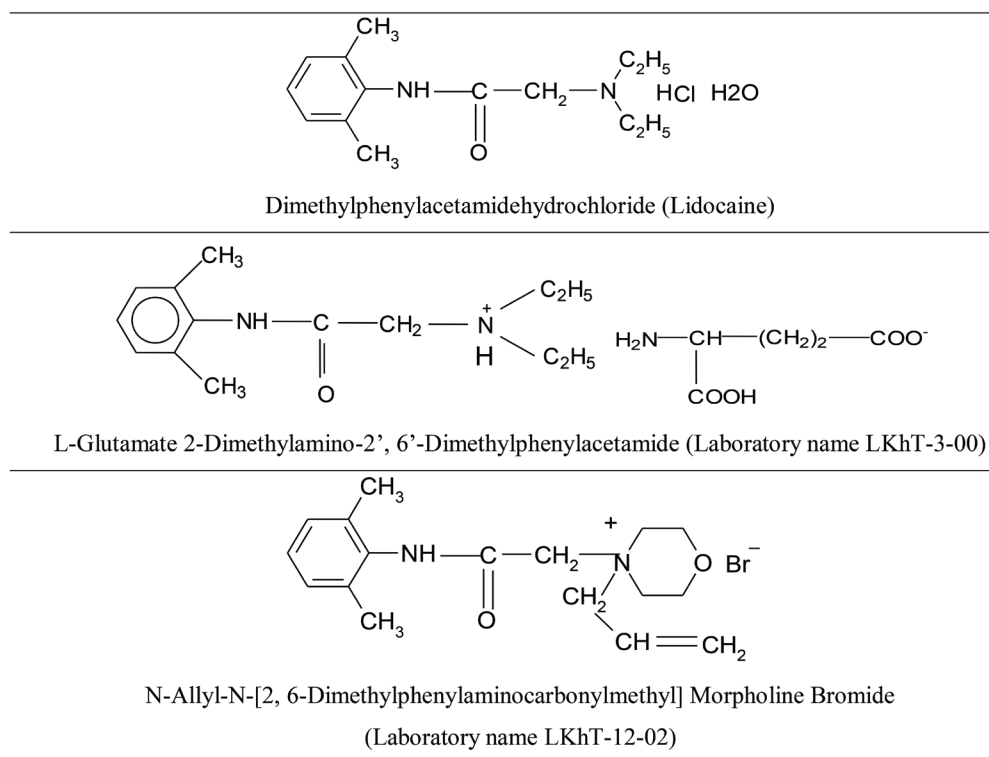


Figure 1. Chemical structures of DPA compounds

tylcholine disturbances of the cardiac rhythm, the reference drug used was the natural alkaloid atropine. When studying the adrenergic component in the mechanism of cardiotropic action of tertiary and quaternary dimethylphenylacetamide (lidocaine) derivatives, $\beta_{1,2}$ -adrenoblocker propranolol was used as a reference drug. To reproduce the acetylcholine arrhythmia, acetylcholine chloride (SIGMA company, Germany) was used; the induction of aconitine rhythm disturbances in the cardiac activity was carried out with the help of alkaloid aconitin from the same manufacturer.

Experimental methods

The role of the cholinergic influence on the derivatives antiarrhythmic actions was identified in a model of AC-induced AF (David and Chick 1951) in the modification in rats. The level of antiadrenergic activity of the compounds was measured in the experiments in mice by using the Moore et al. (1986) method (Moore and Spear 1984). Epinephrine and Norepinephrine concentration in cardiac tissue of rats with acute myocardial ischemia was detected fluorimetrically. The antioxidant activity of LKhT-3-00 and LKhT-12-02 was explored by induced chemical luminescence.

To study the mechanisms of membrane permeability, the BLM permeability coefficients for tertiary and quaternary dimethylphenylacetamide derivatives in the form of ions were measured. By measuring the ion permeability index, BLM permeability was assessed for the derivatives as ions. The BLM permeability for the compounds under

study as ion pairs (neutral compounds) was calculated theoretically - presuming that, as well as for non-electrolytes, BLM permeability depended on the hydrophobic property of the substance. Permeability was estimated by a change in the refractivity of isolated preparations of the right ventricular heart tissue of male rats. The permeability of the lipid membrane for ions - tertiary and quaternary dimethylphenylacetamide derivatives - was determined by the current magnitude of a short-circuit occurring in response to adding the compound on one side of the membrane.

The effect of the test compounds *in vitro* on the depolarisation rate of the leading edge of the action potential (V_{max}), on the amplitude of the action potential and on the duration of the action potential was studied in experiments on papillary muscles (Sakmann and Neher 2009). The effect of dimethylphenylacetamide (Lidocaine) derivatives on the activity of potassium channels was studied by recording the action potentials on gigantic neurons isolated from the peripheral ganglionic ring of the mollusc *Limnea stagnalis* by the patch-clamp method (Beyder et al. 2012).

In experiments in isolated papillary muscular stripes, the authors studied how the compounds affected AP duration, its front extent and velocity of depolarisation (V_{max}) (Sakmann and Neher 2009). The potassium current through Kv4.3-channels was assessed by the patch-clamp method in gigantic neurons of *Limnea stagnalis* mollusc's parapharyngeal ganglion (Beyder et al. 2012).

The significance of the obtained results was estimated with modern statistics methods using licensed PC interface "BioStat", SPSS on a MacBook Air laptop (USA).

Results and Discussion

At the first stage of the study, the preventative and therapeutic activities of the compounds were assessed on the model of aconitin-induced AF (Fig. 2). According to the method description, a few seconds after AC *iv* arrhythmogen infusion and a simultaneous mechanical irritation of the atrium, the onset of arrhythmia was observed lasting 536 ± 12 under control (Fig. 2). In all the experiments, 0.1 mg/kg Atropine Sulphate *iv*, either before or immediately after the arrhythmia commencement, prevented or controlled it. Unlike Atropine, both compounds when infused *iv* demonstrated no significant results. Thus, it could be concluded that tertiary and quaternary DPA derivatives possessed no cholynolytic activity.

Two approaches were used to evaluate the LKhT-3-00 and LKhT-12-02 sympathotropic activity. The first one, similar to that mentioned above, allowed the authors to assess the pharmacological effectiveness of the derivatives in preventing Epinephrine-induced arrhythmia in mice in comparison with Propranolol (Table 1).

Both derivatives prevented considerably reduced chances of development of Epinephrine-induced arrhythmia caused by *iv* administration of 100 $\mu\text{g}/\text{kg}$ Epinephrine with simultaneous Halothane tracheal instillation, therefore demonstrating an effect similar to Propranolol. It was only the tertiary compound LKhT-3-00 which not only had an arrhythmic effect, but also increased the survival rate and life expectancy in mice.

The other way to evaluate antiadrenergic activity of DPA derivatives was to detect the level of Epinephrine and Norepinephrine in the myocardial tissue of rats with acute ischemia. When an occlusive syndrome develops in the myocardium of the ischemia zone, the concentration of both adrenaline and norepinephrine increases (Table 2).

Quaternary DPA compound LkhT-12-02, when administered in a dose of 4.1 mg/kg *iv*, had no effect on the hormones' concentration in the heart tissue. Tertiary DPA

compound LkhT-3-00, in a dose of 8.3 mg/kg, can inhibit the growth of the level of norepinephrine in the damaged area with preventative intravenous administration, without affecting the concentration of adrenaline. And taking into account the fact that norepinephrine in the myocardium is predominantly synaptic in origin, unlike adrenaline coming from the blood plasma, it is reasonable to assume that compound LKhT-3-00 has some adrenergic properties, which can be realised indirectly through exciting glutamate NMDA receptors of cardiomyocytes, which are functionally linked with beta-1-adrenergic receptors (Zhenglin et al. 2012).

An extremely important element, ensuring the pharmacological effect of antiarrhythmics, is its interaction with the cytoplasmic membrane of the cardiomyocyte. It does have particular importance for DPA derivatives as they likely block sodium channels. Sodium current blockers are known to block the sodium channels from the inside of the heart cell membrane and so, to be effective, they should penetrate well through the lipid bilayer (Becker and Reed 2006). The permeability of dimethylphenylacetamide (Lidocaine) derivatives through BLM was assessed by the change in the refractivity of the myocardium strips of the right ventricle of the rat's heart, perfused with solutions of the compounds (Fig. 3).

As a result, Lidocaine, as well as its derivatives, prolonged the refractory period of myocardial strips; therefore both tertiary and quaternary dimethylphenylacetamide (lidocaine) derivatives penetrate through the membrane. However, to evaluate membrane permeability, it became critical to compare the change rate of the myocardial tissue refractory with the estimated velocity of the derivatives entering a cell, assuming that the membrane lipid bilayer limited the flow of the derivatives. When carrying out the calculations, it was found that, while the refractivity change rate for tertiary derivative of LKhT-3-00 corresponded to the rate of entry into the cell (proportional to the extraction coefficient from the octanol-water system),

Table 1. Evaluation of Anti-adrenergic Effect of Tertiary and Quaternary DPA derivatives in experiments on anaesthetised mice

No	Pharmacologic agent	Dose (mg/kg)	Number of animals				Life duration, min, M \pm SD
			Total	VA	CCD	Dead	
1	Control group	-	8	8	8	8	12 \pm 2
2	Propranolol	5.0	8	2#	3#	5	27 \pm 2*
4	Lidocaine	10.0	8	3#	8	7	13 \pm 2 ^a
5	LKhT-3-00	8.3	8	2#	5	3#	21 \pm 3*
6	LKhT-12-02	4.1	8	3#	6	7	14 \pm 3 ^a

Note: VA - ventricular arrhythmia, CCD - cardiac conduction disease

- differences when comparing the results with the "Control group" results are significant at $p < 0.05$, Fisher's exact test.

* - differences when comparing the results with "Control group" results are significant at $p < 0.05$;

^a - when comparing with the "Propranolol" group, the differences are statistically significant at $p < 0.05$ (analysis of the survival curves using the Gehan criterion with Yates' correction).

Table 2. Determination of Epinephrine and Norepinephrine in Myocardium of Rats' hearts during Experimental Ischemia with Administration of DPA derivatives

	Test unit	Experimental group		
		Control group, $\mu\text{M/g}$	LKhT-12-02, $\mu\text{M/g}$	LKhT-3-00, $\mu\text{M/g}$
Norepinephrine	RZ LV	0.43±0.06	0.47±0.12	0.39±0.10
	IZ LV	1.23±0.13*	0.98±0.09*	0.82±0.17*
	LA	0.81±0.15	0.78±0.08	0.84±0.12
Epi-nephrine	RZ LV	0.35±0.08	0.33±0.05	0.37±0.06
	IZ LV	0.96±0.09*	0.76±0.17	0.44±0.07#
	LA	0.49±0.10	0.53±0.08	0.45±0.11

Note: LV - left ventricle, LA - left atrium, RZ - remote zone, IZ – ischemic zone

* - statistical significance of the differences when compared with the “LV group” at $p < 0.05$ is determined using a one-dimensional analysis of variance and the subsequent application of the Newman-Keuls criterion.

- statistical significance of the differences when compared with the “Control” group at $p < 0.05$ is determined using a one-dimensional analysis of variance and the subsequent application of the Newman-Keuls criterion.

for the quaternary derivative of LKhT-12-02, no such regularity in the ionised form was established. At the same time, the issue of membrane permeability for charged molecules of quaternised drugs has long been debated both in foreign and national literature. Sunami at al. (2000) and Tsuchia and Mizogami (2013) proposed a different variant of transporting charged derivatives – transporting them in an electrically neutral form. Such a possibility was repeatedly discussed in literature; however, there has been no single point of view on this topic formed.

According to such an approach, the authors considered an ion pair in a membrane as a neutral molecule of nonelectrolyte composed of the charged quaternary dimethylphenylacetamide (Lidocaine) derivative LKhT-12-02 under study and the basic electrolyte anion Cl⁻. The subsequent calculation proved the assumption that LKhT-12-02 permeates through the cardiomyocyte membrane in the electro-neutral form – in the form of ion pairs.

The functional condition of trans-membrane ion channels amongst other factors depends on a membrane microstructure at a given moment of time. The membrane fluidity or rigidity depends on the functioning of free radical peroxidation systems and anti-oxidation protection.

The influence of tertiary and quaternary DPA derivatives was explored on lipid peroxidation processes in the rat's heart myocard in a model vitelline system (Table 3).

It was found that the prophylactic *iv* administration of the derivatives and the reference drug of Lidocaine inhibits the activation of free radical lipoperoxidation in response to the development of ischemic syndrome. A similar effect for Lidocaine has already been described in foreign scientific periodicals (Kaczmarek et al. 2009, Lenfant et al. 2004). Besides, it should be that the tertiary compound of LKhT-3-00 can simultaneously activate the antioxidant membrane systems which, in case of an occlusal syndrome, would restore the balance of the systems of cardiomyocyte membranes under study. In the experiments on rats with occlusion of the coronary artery, it was also confirmed that LKhT-3-00, when administered *iv* in a dose of 8.3 mg/kg, corrected acidosis and normalised the ratio of the partial oxygen tension and carbon dioxide in the blood of the coronary venous sinus.

At the final stage of the study, it was extremely important to investigate how DPA compounds influenced sodium and potassium ion currents. First of all, an indirect way was used to assess Na⁺-blocking activity of the

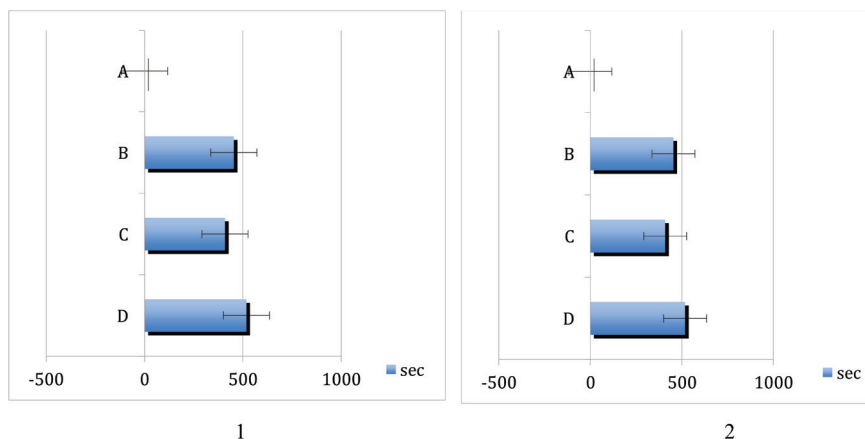


Figure 2. Average duration of AC-induced AF with preventative (1) and controlling (2) *iv* administration of atropine sulphate (A), compound LKhT-3-00 (B), compound LKhT-12-02 (C); D - control group of animals

compounds on the aconitin model of arrhythmias. There, the expected results were obtained proving that both derivatives prevented the generation of aconitine arrhythmia at a wide range of doses and, in terms of the therapeutic effect range, they were not inferior, but rather superior to the reference preparation Lidocaine. In experiments in mice with Aconite-induced arrhythmia, both compounds like Lidocaine demonstrated dose-dependent antiarrhythmic effects.

Moreover the antiarrhythmic index, calculated on basis of the results, showed the compounds effectiveness in doses less than that of Lidocaine.

In the experiments on isolated strips of the right ventricle myocardium of the heart of rats, the changes in some AP parameters against perfusion with solutions containing compounds LKhT-3-00 and LKhT-12-02 (Fig. 4) were studied.

Thus, at 10 mg/ml concentration of LKhT-3-00 and LKhT-12-02, the AP front extent and depolarisation velo-

city (V_{max}) were lowered. At the same time, none of the compounds affected the AP duration measured at 80% depolarisation level. Obtained results proved the anti- Na^+ activity of the DPA derivatives and their K^+ -blocking properties were made doubtful.

Both substances reduced the AP amplitude and suppressed the rate of increase of its leading edge. At the same time, no experiment demonstrated an increase in the AP duration, measured at 80% repolarisation level. The obtained results proved the anti- Na^+ activity of the compounds and questioned the ability of the compounds to suppress or activate the potassium current.

To test this type of activity, the “patch-clamp” technology was used – a method of recording the potential of single potassium channels of a giant neuron isolated from the peripheral ganglionic ring of a large mollusc *Limnea stagnalis*. The potassium channels of this neuron are channels of delayed rectification of type $K_v4.3$, including those present in the myocardium of warm-blooded

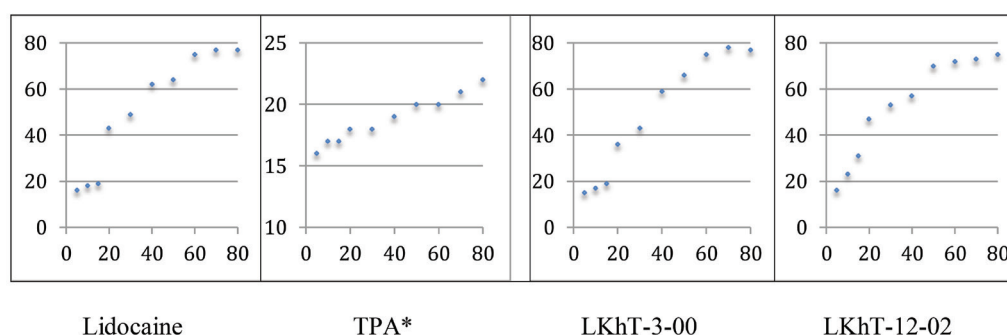


Figure 3. Relative increase in the refractivity of the ventricular heart tissue of the rat (in % of the original value) affected by: 15 μ M lidocaine (n = 5), 50 μ M trimecaine (n = 4), 5 μ M LHT-12-02 (n = 6) and 30 μ M LHT-3-00 (n = 5).

Note: mean refractivity in the control: 92 ± 3 (lidocaine), 90 ± 7 (trimecaine), 94 ± 8 (LKhT-12-02) and 96 ± 4 ms (LKhT-3-00). The average values and root-mean-square deviations are provided. On the abscissa - the time of registration of parameters in min.

* - according to O.G. Agenosova

Table 3. Correlation of Pro-oxidant / antioxidant Potential of Cardiomyocyte Membranes of Rat’s Hearts with Acute Myocardial Infarction, with Dimethylphenylacetamide (Lidocaine), Derivatives Being Preventatively Administered.

Attack intensity, imp/sec	Drug, dose (mg/kg)	Location		
		LA	LV RZ	LV IZ
Oxidative process	Control group	4.77 \pm 1.24	12.8 \pm 0.97	48.5 \pm 3.23
	Lidocaine, 7.6	4.81 \pm 1.12	11.9 \pm 1.04	31.5 \pm 1.18*
	LKhT-3-00, 3.8	5.01 \pm 0.83	9.94 \pm 1.13	30.3 \pm 1.15*
	LKhT-12-02, 1.9	4.96 \pm 1.29	10.5 \pm 0.76	35.7 \pm 0.96*
Antioxidant activity	Control group	3.13 \pm 0.54	3.9 \pm 0.41	14.9 \pm 1.17
	Lidocaine, 7.6	3.26 \pm 0.42	4.1 \pm 0.67	16.3 \pm 2.05
	LKhT-3-00, 3.8	3.09 \pm 1.01	4.3 \pm 1.15	27.3 \pm 2.08 ^q
	LKhT-12-02, 1.9	3.17 \pm 0.23	3.7 \pm 0.94	15.3 \pm 1.73

Note: LA - left atrium, LV - left ventricle, RZ - remote zone, IZ - ischemic zone;

* when compared with the control group, the results are statistically significant at $p < 0.05$ (single-factor analysis of variance, Newman-Keuls criterion);

^q In comparison with the control group, the “Lidocaine” and “LKhT-12-02” groups, the results are statistically significant at $p < 0.05$ (single-factor analysis of variance, Newman-Keuls criterion).

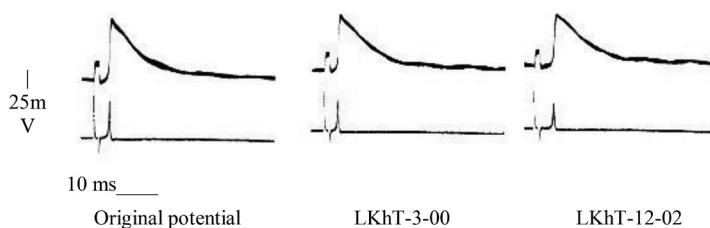


Figure 4. Effect of dimethylphenylacetamide derivatives (at a concentration of 10.0 mg/l) on AP (upper curve) and V_{max} (bottom curve) of the papillary muscle of the rat’s right heart ventricle.

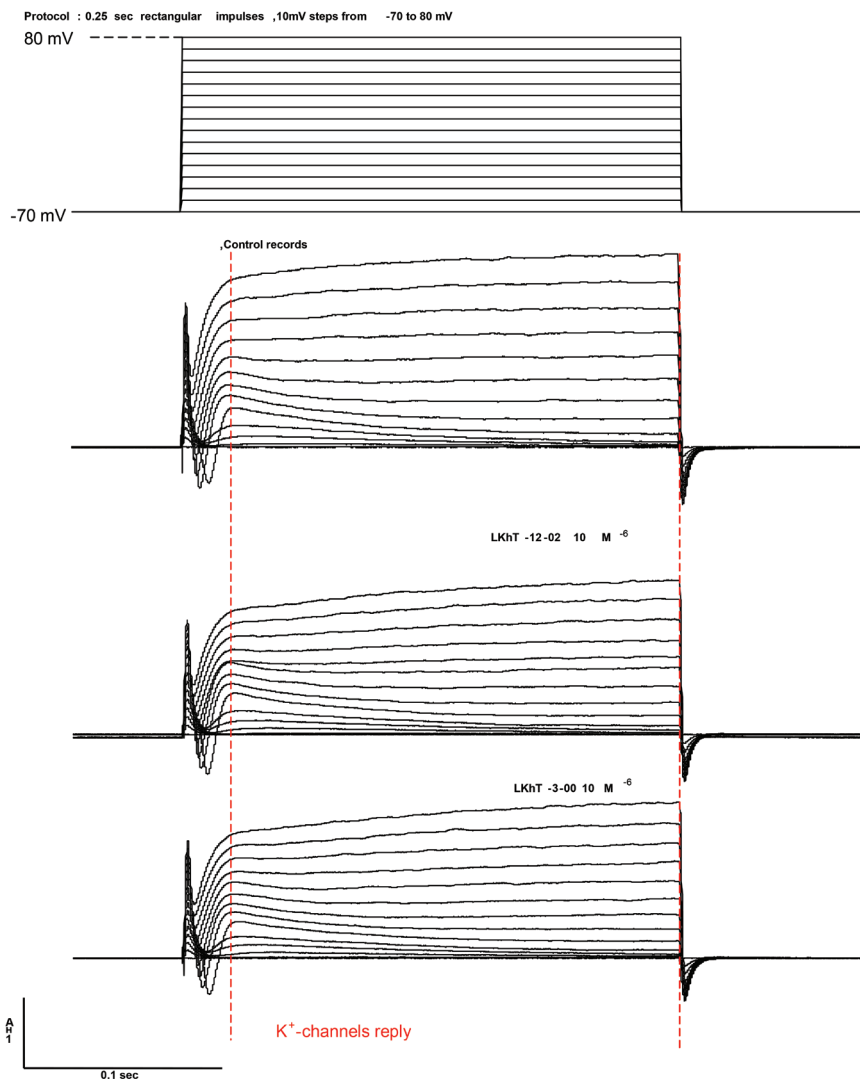


Figure 5. Records of currents through potassium channels of the neuron of the *Limnea stagnalis* mollusc in a “whole-cell” configuration.

mammals and humans. The experiments were carried out in the Laboratory of Cellular Neurobiology of the Institute of Cell Biophysics of the Russian Academy of Sciences, in collaboration with Ph.D., Senior Research Fellow, Maksim E. Astashev.

Cells dialysis was carried out with a solution containing the test derivatives in a concentration range of 10^{-6} to 10^{-4} M. In none of the cells under study (inside-out, single attached cell), neither the tertiary dimethylphenylaceta-

mid (Lidocaine) derivative nor the quaternary derivative changed the functional activity of potassium channels (Fig. 5).

Experiments were conducted in scientific collaboration with Dr. M.E. Astashev¹. The authors dialysed the cell with the derivative-containing solution from 10^{-6} up

¹ Laboratory of Cell Neurobiology of The Institute of Cell Biophysics, Russian Academy of Sciences

to 10^{-4} M concentrations in the following configurations: “whole cell”, “inside-out” and “single-attached cell”. As a result, neither tertiary derivative LKhT-3-00 nor quaternary compound LKhT-12-02 blocked the K^+ -current while it was applied to the inside or outside surface of the channel-containing membrane.

Conclusions

According to the obtained data, the following conclusions can be made:

1. Both tertiary dimethylphenylacetamide (Lidocaine) derivative containing remains of L-Glutamic acid and quaternary Allylmorpholine DPA compound have no cholinergic properties. Tertiary derivatives LKhT-3-00 demonstrate an Epinephrine-negative effect, preventing Epinephrine-induced arrhythmia and experimental animals' mortality as well as lowering an ischemia-mediated increase of Norepinephrine concentration in the heart tissue of rats.
2. LKhT-3-00 pass through the cardiac cell BLM in an ionised form whereas molecules of quaternary dimethylphenylacetamide (Lidocaine) derivative LKhT-12-02 permeate the membrane as an ion pair in an electro-neutral condition.
3. Both tested derivatives restrain the lipid peroxidation process in the ischemic myocardium of rats, but only

the tertiary dimethylphenylacetamide (Lidocaine) derivative LKhT-3-00 was able to activate the antioxidant mechanism, to prevent ischemia-induced acidosis development and to optimise the O_2 and CO_2 concentration in the blood of the coronary venous sinus.

4. Tertiary (LKhT-3-00) and quaternary (LKhT-12-02) ammonium derivatives of dimethylphenylacetamide suppress the generation of arrhythmia caused by the inactivation of sodium channels of cardiomyocytes under the influence of aconitin nitrate, the rate of increase in the leading edge of AP of strips of rats' heart myocardium and its amplitude, showing the properties of sodium channels blockers.
5. The tested dimethylphenylacetamide (Lidocaine) derivatives have no affect on the functional state of potassium channels of delayed rectification either from the outer or inner side of the cell membrane.

Thus, the tested DPA compounds belong to class I of antiarrhythmic drugs with pronounced cytoprotective properties.

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References

- Balashov VP, Blinov DS, Kazachenko VN, Astashev ME, Agenosova OG (2005) Membrane Mechanisms of Antiarrhythmic Effect of Quaternidine. *Bulletin Of Experimental Biology And Medicine*. [Byulleten' ehksperimental'noy biologii i mediciny] 139(6):688-691. [Russian]
- Becker DE, Reed KL (2006) Essentials of Local Anesthetic Pharmacology. *Anesthesia Progress*. 53(3): 98–109. doi: [https://doi.org/10.2344/0003-3006\(2006\)53\[98:EOLAP\]2.0.CO;2](https://doi.org/10.2344/0003-3006(2006)53[98:EOLAP]2.0.CO;2) [PMC]
- Beyder A, Stregre PR, Bernard C, Farrugia G (2012) Membrane Permeable Local Anesthetics Modulate $Na_v1.5$ mechanosensitivity. *Channels*. 6(4): 308-316. doi: [10.4161/chan.21202](https://doi.org/10.4161/chan.21202) [PMC]
- Blinov DS, Sernov LN, Skachilova SY, Belova LA, Balashov VP, Astashev ME, Druginina VV, Shilova EV (2004) Quaternary Ammonium Lidocaine Derivative with Antiarrhythmic Activity and a Way for Obtaining it. Russian Federation patent 2258700. [Russian]
- Blinov DS, Singh LN, Elizarova JN, Blinova EV, Skachilova SYa, Salamova EI, Meleshkin AI (2014) Comparative Study of Toxicity and Antiarrhythmic Activity of Some Organic Derivatives of Dimethylacetamide. *Experimental and Clinical Pharmacology*. [Ekspperimental'naya i klinicheskaya farmakologiya]. 77(5): 20-22. [Russian]
- Blinova EV, Skachilova SYa, Blinov DS, Singh LN, Elizarova YN, Meleshkin AI, Ivanova EA, Salyamova EI (2015) A Comparative Study of Toxicity and the Scale of Activity of New N-Substituted Benzamide Derivative. *Journal Of New Medical Technologies*. [Vestnik Novyh Mediczinskih tehnologiy]. 22(1): 16-19. [Russian]
- Castro UV, Toquero RJ, Fernandez LJ (2015) Preventing Recurrences: Classic and Modern Antiarrhythmic Drugs in Atrial Fibrillation. *Cardiol. Pharmacol.* (4): 130-138. doi: [10.4172/2329-6607.1000130](https://doi.org/10.4172/2329-6607.1000130) [Full text]
- Collinsworth KA, Kalman SM, Harrison DS (1974) The Clinical Pharmacology of Lidocaine as an Antiarrhythmic Drug. *Circulation*. (50): 1217-1231. [Full text]
- David S, Chick FB (1951) Abnormal cardiac rhythms caused by acetylcholine. *Circulation*. (3): 764. doi: [10.1161/01.CIR.3.5.764](https://doi.org/10.1161/01.CIR.3.5.764) [Full text]
- Kaczmarek DJ, Herzog C, Larmann J. et al (2009) Lidocaine Protects from Myocardial Damage due to Ischemia and Reperfusion in Mice by its Antiapoptotic Effects. *Anesthesiology*. 110(5): 1041-1049. doi: [10.1097/ALN.0b013e31819dabda](https://doi.org/10.1097/ALN.0b013e31819dabda) [Full text]
- Lenfant F, Lahet J, Courderot-Masuyer C, Freysz M, Rochette L (2004) Lidocaine Has Better Antioxidant Potential Than Ropivacaine and Bupivacaine: in vitro Comparison in a Model of Human Erythrocytes Submitted to an Oxidative Stress. *Biomedicine and Pharmacotherapy*. 58(4): 248–254. doi: [10.1016/j.biopha.2003.12.013](https://doi.org/10.1016/j.biopha.2003.12.013) [Full text]
- Marasanov SB, Lebedev AB, Chkhatval NA, Blinov DS, Hamidullina ZD, Puchkova TA (2013a) Potentials of Search for New

- Antiarrhythmic Agents. Volga Medical Journal. [Verhnevolgskiy Mediczinskiy Zhurnal], 11(1): 25-29. [Russian]
- Marasanov SB, Lebedev AB, Chkhatval NA, Blinov DS, Hamidulina ZD, Puchkova TA (2013b) Possibility of Search for New Antiarrhythmic Agents. Tver Medical Journal. [TverskoyMediczinskiy Zhurnal], 2(1): 16-27. [Russian]
 - Moore EN, Spear JF (1984) Acute Animal Models for the Study of Antiarrhythmic Drugs for the Prevention of Sudden Coronary Death. In: Lucchesi BR, Dingell JV, Schwarz RP Jr. (Ed) Clinical Pharmacology of Antiarrhythmic Therapy. Raven Press, NY. 31–46. [Full text]
 - Sernov LN, Skachilova SYa, Druzhinina VV, Shilova EV, Blinov DS, Kostin YaV (2005) *Synthesis and Antiarrhythmic Activity of 2-Diethylamino-2,6-Dimethylphenylacetamide Derivatives*. *Pharmaceutical Chemistry Journal*. 39(7): 350-353.
 - Sakmann B, Neher E (2009) *Single-channel Recording*. Second ed. Springer Science-Business Media LLC; 384 p. [Full text]
 - Sunami A, Glaaser IW, Fozzard HA (2000) A Critical Residue for Isoform Difference in Tetrodotoxin Affinity is a Molecular Determinant of the External Access Path for Local Anesthetics in the Cardiac Sodium Channel. *Proceedings of the National Academy of Sciences of the United States of America*. 97(5): 2326–2331. [Full text]
 - Tsuchia H, Mizogami M (2013) Interaction of Local Anesthetics with Biomembranes Consisting of Phospholipids and Cholesterol: Mechanistic and Clinical Implication of Anesthetic and Cardio-toxic Effect. *Anesthesiol. Res. And Pract.* article ID 297141.
 - Zhenglin G, Wenhua L, Jing W, Zhen Y (2012) Regulation of N-Methyl-D-aspartic Acid (NMDA) Receptors by Metabotropic Glutamate Receptor 7. *J Biol. Chem.* 287(13): 10265–10275. doi: 10.1074/jbc.M111.325175 [PMC]

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