Cellular and Molecular Neurobiology (2021) 41:395–401
https://doi.org/10.1007/s10571-020-00840-3

BRIEF COMMUNICATION

Adrenaline Facilitates Synaptic Transmission by Synchronizing Release of Acetylcholine Quanta from Motor Nerve Endings

Venera Khuzakhmetova[1] · **Ellya Bukharaeva**[1]

Received: 3 November 2019 / Accepted: 1 April 2020 / Published online: 9 April 2020

Abstract

The long history of studies on the effect of catecholamines on synaptic transmission does not answer the main question about the mechanism of their action on quantal release in the neuromuscular junction. Currently, interest in catecholamines has increased not only because of their widespread use in the clinic for the treatment of cardiovascular and pulmonary diseases but also because of recent data on their possible use for the treatment of certain neurodegenerative diseases, muscle weakness and amyotrophic sclerosis. Nevertheless, the effects and mechanisms of catecholamines on acetylcholine release remain unclear. We investigated the action of noradrenaline and adrenaline on the spontaneous and evoked quantal secretion of acetylcholine in the neuromuscular junction of the rat *soleus* muscle. Noradrenaline (10 μM) did not change the spontaneous acetylcholine quantal release, the number of released quanta after nerve stimulation, or the timing of the quantal secretion. However, adrenaline at the same concentration increased spontaneous secretion by 40%, increased evoked acetylcholine quantal release by 62%, and synchronized secretion. These effects differ from those previously described by us in the synapses of the frog *cutaneous pectoris* muscle and mouse *diaphragm*. This indicates specificity in catecholamine action that depends on the functional type of muscle and the need to take the targeted type of muscle into account in clinical practice.

Keywords Neuromuscular junction · Quantal acetylcholine release · Catecholamine · Timing of the evoked quantal secretion

Introduction

There are at least three main reasons for the increased interest in catecholamine action on synaptic transmission in the neuromuscular junction over the last decade. First, there have been many studies confirming the effectiveness of adrenergic compounds in treating a wide range of neurodegenerative diseases. Well-known drugs used for cardiovascular and pulmonary pathologies started being offered for the treatment of congenital myasthenic syndromes (Legay 2018; Engel et al. 2015), anti-MuSK myasthenia gravis (Burke et al. 2013; Ghazanfari et al. 2014), and amyotrophic lateral sclerosis (Bartus et al. 2016). Second, direct evidence of tight contact of sympathetic axons with neuromuscular junctions has been obtained. Rudolf et al. (2013), Khan et al. (2016), Straka et al. (2018) and Rodrigues et al. (2019a) have shown, using modern immunofluorescence methods, that sympathetic innervation controls homeostasis of neuromuscular junctions. The third reason is the contradictory data and unclear mechanisms of catecholamine action on synaptic transmission (for review see Tsentsevitsky et al. 2019a).

Differences have been revealed in the effects of adrenaline (AD) and noradrenaline (NA) on both spontaneous quantal secretion and the number of quanta released in response to a nerve stimulus (quantal content). The variability of the observed effects of catecholamines may be due to different types of muscles (e.g., fast and slow, fatigued and intact), different species of animals, various experimental conditions (inhibition of acetylcholinesterase, various methods of blocking muscle contractions, preliminary nerve ending polarization). Joassard et al. (2013) established that skeletal muscle hypertrophy induced by adrenomimetics is associated with changes in the composition of skeletal muscle fibres. A decrease in the proportion of slowly contracting fibres and a corresponding increase in the proportion of fast fibres in rat skeletal muscles in response to the action of

✉ Venera Khuzakhmetova
venerik87@mail.ru

[1] Kazan Institute of Biochemistry and Biophysics FRC Kazan Scientific Center of RAS, Kazan, Russia

adrenomimetics were described. Such a switch in muscle fibres is particularly pronounced in a typical slow muscle of the hind limbs, the *soleus* muscle (Soić-Vranić et al. 2005). Recently, we described the features of the action of NA and AD in diaphragm synapses, consisting of fast and slow fibres (Tsentsevitsky et al. 2019b). Therefore, it was interesting to evaluate how exogenous adrenomimetics affect the synapses of a muscle containing fibres of the slow type, which *M. soleus* is.

Here, we investigated AD and NA action on the parameters of acetylcholine (ACh) quantal release—frequency of spontaneous miniature endplate potentials (F MEPPs), quantal content of the evoked endplate potentials (QC EPPs) and degree of synchrony of the release evoked by a single action potential at the neuromuscular junction in the rat slow *soleus* muscle.

Materials and Methods

Experimental Animals

Experiments were performed on isolated nerve-muscle preparation *M. soleus* of laboratory rats (10–12 months) of the Wistar strain of both sexes weighing 200–250 g. A Ringer solution of the following composition was used (in mM): NaCl, 120.0; KCl, 5.0; $CaCl_2$, 0.4; $NaHCO_3$, 11.0; $NaHPO_4$, 1.0; $MgCl_2$, 5.0; glucose, 11; pH 7.2–7.4; and temperature of 20 ± 0.3 °C (Bukharaeva et al. 2007). The solution was bubbled with 95% O_2 and 5% CO_2. The solution flowed through the muscle chamber continuously at the rate of 5 ml/min.

Electrophysiology

The motor nerve was stimulated with suprathreshold stimuli at a frequency of 0.5 Hz. The nerve ending action currents and endplate potentials (EPPs) were simultaneously acquired in the endplate region. Extracellular pipettes (tip diameter of 2–3 µm, input resistance of 1–3 MΩ) were positioned in the endplate region under microscope control. Spontaneous miniature EPPs (MEPPs) were recorded during the interstimuli intervals, and the averaged MEPP frequency was estimated. The ratio n/N was used as the estimate of the EPP quantal content (QC), where n is the number of successive EPPs, and N is the number of applied stimuli (Katz and Miledi 1965). The experiment lasted 1.5–2 h. A time control was carried out, which showed that the parameters of the signals during this time did not significantly change. Synaptic signals were acquired in control conditions and 20 min after the application of the drug-containing solution. The acquired signals were filtered between 0.03 Hz and 10 kHz, digitized at 3-µs intervals by a 9-bit analogue–digital converter, fed into the computer and processed by original homemade software. The methods for extracellular recordings and data acquisition and processing have been previously described in detail (Bukcharaeva et al. 1999; Bukharaeva et al. 2007; Tsentsevitsky et al. 2018). Synaptic delay was measured as the time interval between the peak of the inward presynaptic Na^+ current and the time at which the rising phase of the quantal event reached 20% of its maximum (Katz and Miledi 1965; Bukcharaeva et al. 1999). Measured time parameters are shown in Fig. 2b. The limit of the synaptic delay measurement was set to 50 ms. The stability of the recording electrode position was crucial during long-term extracellular recordings. We therefore monitored the amplitudes of the nerve terminal action potentials throughout each dataset. Only experiments in which the terminal action potential changed by less than 10% during the drug application and washout were analysed (Bukcharaeva et al. 1999; Bukharaeva et al. 2007). Because the distribution of delays was not normal, the average value of synaptic delays could not be used. Histograms of the delays' distribution were constructed. To ensure that the number of recorded uni-quantal EPPs in the 10-ms period did not depend on the variability in different preparators, the number of collected signals was normalized to an equal number of stimulations (1000 stimuli).

Drugs

Solutions of 10 µM NA ((±)-norepinephrine (+)-bitartrate salt, Sigma–Aldrich, USA) and 10 µM L-adrenaline TCI Chemicals (Tokyo, Japan) were prepared immediately before the experiment. We conducted experiments under darkened conditions and did not observe a colour change in the adrenaline and noradrenaline solutions due to oxidation.

Statistical Analysis

The data are presented as the means ± SEM. The significance of the mean value differences was assessed by Student's t test and the Wilcoxon signed-rank test for matched samples. The results were considered significantly different at $p < 0.05$, where n corresponds to the number of animals.

Results

Catecholamines can undergo autoxidation with the formation of coloured products that have a maximum absorption at 347 and 480 nm (Misra and Fridovich 1972; Palop et al. 2002). The oxidation products of catecholamines (in particular, adrenochrome and adrenolutin) exhibit fluorescence in the yellow-green region of the spectrum. We conducted a special study and compared the absorption and fluorescence spectra of oxidized products in NA solution (10 µM) and

AD solution (10 µM) in control and in a perfusion solution that flowed for 20 min through an experimental bath with a neuromuscular preparation using a Lambda-25 spectrophotometer (Perkin Elmer, USA) and Fluorat-02-Panorama spectrofluorometer (Russia). The absorption and fluorescence spectra (λ_{ab} 510 nm/λ_{em} 550 nm) of the perfusion solution of NA (0.0071 ± 0.0005) and AD (0.0096 ± 0.0012) did not change compared to the control (0.0061 ± 0.0008 and 0.0179 ± 0.0022, respectively), which indicates the absence of significant oxidation of NA and AD molecules under the conditions of our experiments.

The amplitude and time characteristics of the responses did not significantly change with the application of the catecholamines (Table 1). This indicated that there were no effects on the sensitivity of the postsynaptic membrane to ACh.

Parameters of the quantal secretion (average frequency of MEPP and EPP QC) in the control conditions and after application of 10 µM NA or AD are presented in Table 2. The changes in the average MEPP frequency with NA and AD administration are presented in Fig. 1a, b. The frequency of spontaneous ACh quantal release did not change with NA, but it was 40% higher in the presence of AD (Fig. 1d). This effect was eliminated when AD was removed.

NA did not affect the EPP QC, but AD increased the EPP QC by 62% (Fig. 2c, Table 2). Obtained data indicated the presynaptic site of AD action, which changed the process of ACh quantal release.

After motor nerve action potentials, transmitter quanta are released with variable delays. The delay duration reflects the rates of depolarization—release coupling (Katz and Miledi 1965; Lin and Faber 2002), but their dispersion indicates

Table 1 Parameters of spontaneous and evoked endplate potentials after NA and AD application

	Control ($n=9$)	NA ($n=9$)	Control ($n=5$)	AD ($n=5$)
A EPP (mV)	0.11 ± 0.006	0.14 ± 0.02	0.13 ± 0.02	0.14 ± 0.02
A MEPP (mV)	0.10 ± 0.009	0.10 ± 0.01	0.17 ± 0.09	0.14 ± 0.05
RT EPP (ms)	0.34 ± 0.01	0.37 ± 0.01	0.33 ± 0.02	0.35 ± 0.07
RT MEPP (ms)	0.31 ± 0.01	0.33 ± 0.01	0.33 ± 0.02	0.34 ± 0.02
τ EPP (ms)	1.46 ± 0.08	1.72 ± 0.14	1.47 ± 0.14	1.70 ± 0.09
τ MEPP (ms)	1.60 ± 0.16	1.19 ± 0.15	1.69 ± 0.16	1.83 ± 0.10

A EPP (A MEPP) amplitude of EPP (MEPP), *RT EPP (RT MEPP)* rise time of EPP (MEPP), *τ EPP (τ MEPP)* decay constant of EPP (MEPP), *n* number of synapses = number of animals

*$p < 0.05$ compared to control value

Table 2 MEPP frequency and EPP quantal content after NA and AD application

Number of experiments	EPP QC			MEPP frequency		
	Control	NA (10 µM)	Wash out	Control	NA (10 µM)	Wash out
1	0.68	0.77	0.8	0.56	0.63	0.61
2	0.92	0.97	0.95	1.08	1.17	1.02
3	0.38	0.64	0.62	0.77	0.85	0.66
4	0.87	1.26	1.23	0.51	1.03	0.92
5	0.67	0.47	0.4	0.64	0.56	0.6
6	1.06	0.52	0.4	0.22	0.73	0.78
7	1.16	1.35	1.15	0.71	0.3	0.37
8	0.32	0.64	0.74	0.75	1.34	0.02
9	0.77	0.87	0.8	0.6	0.58	0.56
10				0.38	0.55	0.5
Mean ± SE	0.76 ± 0.09	0.83 ± 0.10	0.79 ± 0.10	0.62 ± 0.07	0.77 ± 0.10	0.60 ± 0.09
*p value		$p = 0.47$			$p = 0.16$	
Number of experiments	EPP QC			MEPP frequency		
	Control	AD (10 µM)	Wash out	Control	AD (10 µM)	Wash out
1	0.4	0.69	0.5	1	1	1.03
2	0.18	0.35	0.32	0.57	0.66	0.5
3	0.89	1.1	1.05	0.65	0.96	0.79
4	0.61	1.17	0.87	0.27	0.82	0.65
5	0.69	1.13	–	0.51	1.02	–
Mean ± SE	0.55 ± 0.12	0.89 ± 0.16	0.69 ± 0.17	0.60 ± 0.12	0.89 ± 0.07	0.74 ± 0.11
*p value		$p = 0.01$			$p = 0.049$	

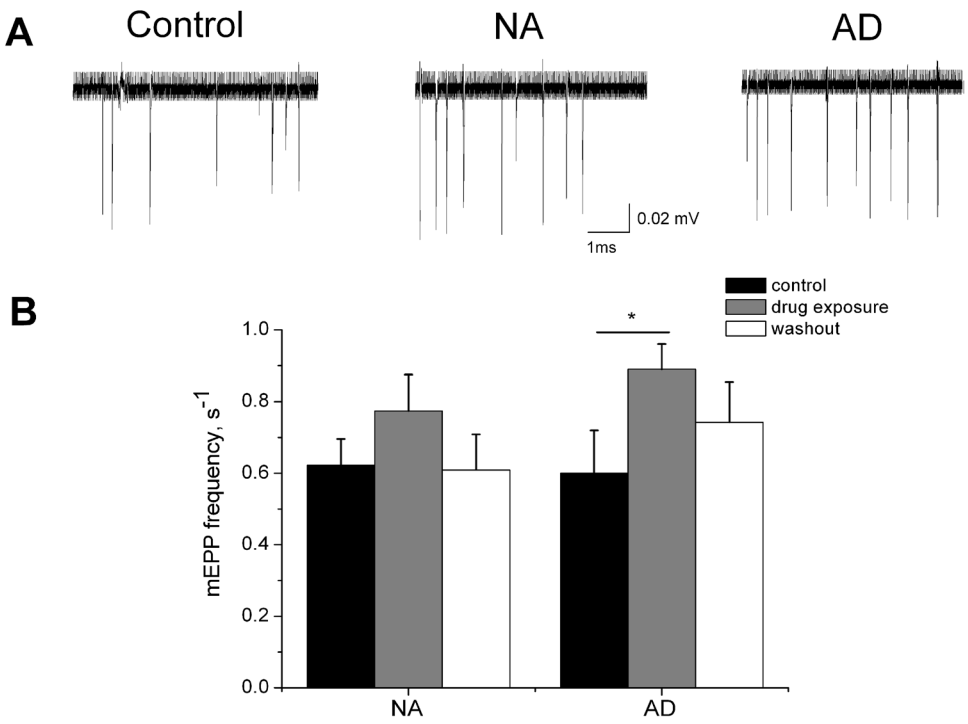

Fig. 1 Changes in spontaneous quantal ACh release after application of NA or AD at a concentration of 10 μM. **a** Trace of spontaneous ACh release (MEPPs) in Ringer solution after NA and AD application. **b** Average MEPP frequencies in control conditions (black columns), with application of NA or AD (grey columns), and after removal of the catecholamines (white columns). $^{*}p < 0.05$ from control value

that evoked phasic quantal release is not synchronous (Bukharaeva et al. 2007; Kaeser and Regehr 2014).

In low Ca^{2+}/high Mg^{2+} external solution conditions, in the synapse of *M. soleus* as well as in the diaphragm (Bukharaeva et al. 2007; Tsentsevitsky et al. 2018), ACh quanta are released with varying synaptic delays after nerve action potential arrival, i.e., asynchronously (Fig. 2a). After the addition of NA, the number of quanta released during 10 ms with the 1000 stimuli did not significantly change (Fig. 2d), whereas AD application led to a decrease in the dispersion of synaptic delays and an increase in the number of responses with short delays, i.e., there were more responses with short delays in the AD than in the control conditions in the histogram of the delay distribution. That is, the secretion became more synchronous (Fig. 2e).

Discussion

In the neuromuscular junction of the rat slow *M. soleus*, we observed the absence of effects of NA at a concentration of 10 μM on parameters of synaptic transmission and the increased spontaneous and evoked quantal secretion in the presence of AD at the same concentration.

Catecholamines can facilitate muscle contraction—this fact was discovered more than a hundred years ago (Oliver and Schäfer 1895). However, the data regarding targeting and the mechanisms of their actions on neuromuscular transmission have been very controversial. Kuba (1970) indicated the facilitation of the action of noradrenaline on the frequency of MEPPs. However, this effect was observed under 20 μM noradrenaline (2 times higher than the concentration we used), and *M. diaphragm* was used. However, it was shown previously that the effects of adrenergic compounds on the synapses of fast and slow types of muscles differ. The activation of β receptors increased the evoked contractions of fast muscles and reduced the contractions of slow muscles (Bowman and Raper 1962, 1967). The magnitude and nature of the adrenergic effects vary depending on the fibre-type composition of the muscle (Juel 1988; Cairns and Dulhunty 1993; Decorte et al. 2015; Cairns and Borrani 2015). Krnjevic and Miledi (1958) wrote about the effects produced by adrenaline upon neuromuscular propagation in rats: "We have found the actions of adrenaline and noradrenaline to be to some extent unpredictable". In addition, the effects of catecholamines on the probability of acetylcholine quanta release from nerve endings depend on the membrane potential of terminals, the concentration of extracellular calcium and the content of sodium or magnesium ions in extracellular solution (Kuba and Tomita 1971; Anderson and Harvey 1988; Ginsborg and Hirst 1971). Therefore, the differences in the experimental conditions and types of neuromuscular junctions may be the reason for the controversial data.

Previously, we found that 10 μM NA had no effect on QC of ACh release evoked by nerve stimulation at both physiological and reduced concentrations of external Ca^{2+} in frog and mouse *diaphragm* neuromuscular junctions (Bukcharaeva et al. 1999; Tsentsevitsky et al. 2018), but NA changed the degree of synchronous quantal release. In this study, we observed that NA was ineffective in the *M.*

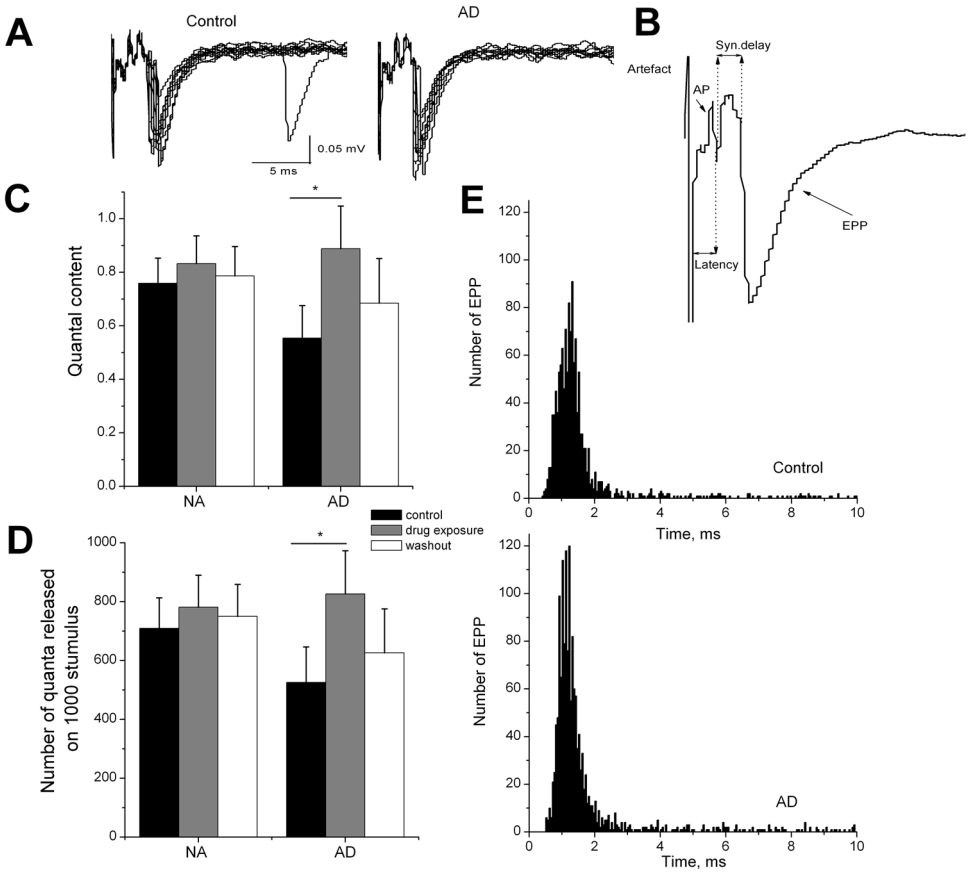

Fig. 2 Action of catecholamines on the evoked quantal ACh release. **a** Superposition of selected uni-quantal EPPs in control conditions and after AD application. **b** Evoked EPP, measured in the experiment: AP—nerve action potential, syn. delay—time interval between peak of AP and the time at which the rise phase of the quanta event reached 20% of its maximum, latency—time interval between the stimulus and peak of AP. **c** Average quantal content in control conditions (black columns), after catecholamine application (grey columns), and after catecholamine removal (white columns). **d** Average number of EPPs released with synaptic latencies not exceeding 3 ms—the period of early synchronous release in control conditions (black columns), after catecholamine application (grey columns), and after catecholamine removal (white columns). **e** Histograms of the synaptic latency distribution in control conditions (upper) and after AD treatment (lower), bin 10 ms

soleus synapse, whilst AD increased the mean EPP QC in response to nerve impulses and evaluated spontaneous secretion. Another important characteristic of the neurosecretion process is the time course of quantal secretion (Katz and Miledi 1965; Barrett and Stevens 1972; Bukharaeva and Nikolskii 2012). The release of several dozen quanta of ACh in response to a single nerve impulse does not occur simultaneously. There is asynchrony during the secretion of individual quanta, manifested by the dispersion of real synaptic latencies of uni-quantal responses recorded under low Ca^{2+}/high Mg^{2+} conditions (Katz and Miledi 1965; Barrett and Stevens 1972). Analysis of the distribution of delays of individual quantal events provides insights into the intraterminal processes determining the time course of release probability (Schneggenburger and Neher 2000; Huang and Moser 2018). Our data indicated that AD shortened the release period for evoked quantal release and that the response became increasingly synchronized. As shown in our investigation of frog synapses, better synchronization of release significantly increased the size of reconstructed multi-quantal EPCs (Bukcharaeva et al. 1999). This suggested that AD facilitated synaptic transmission by making the release of quanta more synchronous.

Questions about the mechanism of AD action remain open. It must be taken into account that there are two types of α and β adrenoreceptors, including 6 subtypes, which have different sensitivities to NA and AD and are associated with different membrane and intracellular systems (potential-dependent calcium channels, potassium channels, adenylate cyclase and cAMP, phospholipase, inositol triphosphate complex) (Bylund 2007; Abdullahi et al. 2019). Previously, we showed the synchronizing effect of NA in frog synapses occurred through β1 adrenoreceptors (Bukcharaeva et al. 1999). In the neuromuscular synapse

of the mouse *diaphragm*, the opposite effect of desynchronization of NA secretion was observed, and both α and β receptors were involved in this action (Tsentsevitsky et al. 2018, 2019b). Thus, to identify the subtype of adrenergic receptors involved in the implementation of the AD effect, a full pharmacological analysis will be carried out using specific agonists and blockers for each receptor subtype. Nevertheless, we have previously shown that the degree of synchronization of secretion in the mouse neuromuscular synapse depended on the entry of calcium ions into the nerve ending. When Ca^{2+} was increased, the synchrony of quantal secretion was increased (Bukharaeva et al. 2007). This relationship arises because intracellular Ca^{2+} determines the forward rate of Ca^{2+}-activated vesicular fusion, such that higher Ca^{2+} accelerates the forward release reaction rate and makes short synaptic latencies (Schneggenburger and Neher 2000, 2005). Therefore, it can be suggested that the synchronizing effect of AD on the secretion of quanta is due to the increased calcium entering the nerve ending. This was confirmed by the observed evaluation of the spontaneous response frequency and an increase in QC. Recent evidence that the β-agonist salbutamol uses the P/Q-type Ca_v channel to enhance neuromuscular transmission (Rodrigues et al. 2019b) confirms this conclusion.

Thus, we may conclude that AD facilitates the neuromuscular junction by increasing calcium entry into the nerve ending and increasing spontaneous ACh release, increasing evoked transmitter release and synchronizing quantal secretion.

Acknowledgements This work was supported by the Russian Science Foundation (Project No. 18-15-00046). The investigation of the catecholamine's autoxidation was supported by government assignment for FRC Kazan Scientific Center of RAS. We are grateful to Svetlana Dmitrieva for her help in doing the catecholamine's autoxidation analysis.

Author Contributions VK and EB contributed equally to the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study conformed to the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, revised 1996) and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other (Int. J. Mol. Sci. 2019, 20, 4860 10 of 17) Scientific Purposes (Council of Europe No. 123, Strasbourg, 1985). The experimental protocol met the requirements of the EU Directive 2010/63/EU and was approved by the Bioethics Committees of Kazan State Medical University (Protocol #3/ 29 Jan 2016).

References

Abdullahi A, Wang V, Auger C, Patsouris D, Amini-Nik S, Jeschke MG (2019) Catecholamines induce endoplasmic reticulum stress via both alpha and beta receptors. Shock. https://doi.org/10.1097/SHK.0000000000001394

Anderson AJ, Harvey AL (1988) Effects of the facilitatory compounds catechol, guanidine, noradrenaline and phencyclidine on presynaptic currents of mouse motor nerve terminals. Arch Pharmacol 338:133–137

Barret EE, Stevens CF (1972) The kinetics of transmitter release at the frog neuromuscular junction. J Physiol 227:691–708

Bartus RT, Bétourné A, Basile A, Peterson BL, Glass J, Boulis NM (2016) β2-Adrenoceptor agonists as novel, safe and potentially effective therapies for amyotrophic lateral sclerosis (ALS). Neurobiol Dis 85:11–24. https://doi.org/10.1016/j.nbd.2015.10.006

Bowman WC, Raper C (1962) Adrenaline and slow-contracting skeletal muscles. Nature 6(193):41–43

Bowman WC, Raper C (1967) Adrenotropic receptors in skeletal muscle. Ann N Y Acad Sci 139(3):741–753. https://doi.org/10.1111/j.1749-6632.1967.tb41241.x

Bukcharaeva EA, Kim KC, Moravec J, Nikolsky EE, Vyskocil F (1999) Noradrenaline synchronizes evoked quantal release at frog neuromuscular junctions. J Physiol 517:879–888. https://doi.org/10.1111/j.1469-7793.1999.0879s.x

Bukharaeva E, Nikolskii E (2012) Changes in the kinetics of evoked secretion of transmitter quanta—an effective mechanism modulating the synaptic transmission of excitation. Neurosci Behav Physiol 42:153–160

Bukharaeva EA, Samigullin D, Nikolsky EE, Magazanik LG (2007) Modulation of the kinetics of evoked quantal release at mouse neuromuscular junctions by calcium and strontium. J Neurochem 100:939–949. https://doi.org/10.1111/j.1471-4159.2006.04282.x

Burke G, Hiscock A, Klein A, Niks EH, Main M, Manzur AY, Ng J, De-Vile C et al (2013) Salbutamol benefits children with congenital myasthenic syndrome due to DOK7 mutations. Neuromuscul Disord 23:170–175. https://doi.org/10.1016/j.nmd.2012.11.004

Bylund DB (2007) Alpha- and beta-adrenergic receptors: Ahlquist's landmark hypothesis of a single mediator with two receptors. Am J Physiol Endocrinol Metab 293(6):1479–1481. https://doi.org/10.1152/ajpendo.00664.2007

Cairns S, Borrani F (2015) β-Adrenergic modulation of skeletal muscle contraction: key role of excitation—contraction coupling. J Physiol 593:4713–4727. https://doi.org/10.1113/JP270909

Cairns SP, Dulhunty AF (1993) The effects of beta-adrenoceptor activation on contraction in isolated fast- and slow-twitch skeletal muscle fibres of the rat. Br J Pharmacol 110(3):1133–1141. https://doi.org/10.1111/j.1476-5381.1993.tb13932.x

Decorte N, Lamalle L, Carlier PG, Giacomini E, Guinot M, Levy P, Verges S, Wuyam B (2015) Impact of salbutamol on muscle metabolism assessed by 31P NMR spectroscopy. Scand J Med Sci Sports 25:e267–e273. https://doi.org/10.1111/sms.12312

Engel AG, Shen XM, Selcen D, Sine SM (2015) Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. Lancet Neurol 14:420–434. https://doi.org/10.1016/S1474-4422(14)70201-7

Ghazanfari N, Morsch M, Tse N, Reddel SW, Phillips WD (2014) Effects of the ß2-adrenoceptor agonist, albuterol, in a mouse model of anti-MuSK Myasthenia Gravis. PLoS ONE 9(2):e87840. https://doi.org/10.1371/journal.pone.0087840

Ginsborg BL, Hirst GD (1971) Prostaglandin E1 and noradrenaline at the neuromuscular junction. Br J Pharmacol 42(1):153–154

Huang CH, Moser T (2018) Ca^{2+} regulates the kinetics of synaptic vesicle fusion at the afferent inner hair cell synapse. Front Cell Neurosci 12:364. https://doi.org/10.3389/fncel.2018.00364

Joassard OR, Durieux AC, Freyssenet DG (2013) β2-Adrenergic agonists and the treatment of skeletal muscle wasting disorders. Int J Biochem Cell Biol 45(10):2309–2321. https://doi.org/10.1016/j.biocel.2013.06.025

Juel C (1988) The effect of β2-adrenoceptor activation on ion-shifts and fatigue in mouse soleus muscles stimulated in vitro. Acta Physiol Scand 134:209–216. https://doi.org/10.1111/j.1748-1716.1988.tb08481.x

Kaeser PS, Regehr WG (2014) Molecular mechanisms for synchronous, asynchronous, and spontaneous neurotransmitter release. Annu Rev Physiol 76:333–363. https://doi.org/10.1146/annurev-physiol-021113-170338

Katz B, Miledi R (1965) The measurement of synaptic delay, and the time course of ACh release at the neuromuscular junction. Proc R Soc Lond B 161:483–495. https://doi.org/10.1098/rspb.1965.0016

Khan MM, Lustrino D, Silveira WA, Wild F, Straka T, Issop Y, O'Connor E, Cox D et al (2016) Sympathetic innervation controls homeostasis of neuromuscular junctions in health and disease. Proc Natl Acad Sci USA 113:746–750. https://doi.org/10.1073/pnas.1524272113

Krnjevic K, Miledi R (1958) Some effects produced by adrenaline upon neuromuscular propagation in rats. J Physiol 141(2):291–304. https://doi.org/10.1038/193041a0

Kuba K (1970) Effects of catecholamines on the neuromuscular junction in the rat diaphragm. J Physiol 211(3):551–570. https://doi.org/10.1113/jphysiol.1970.sp009293

Kuba K, Tomita T (1971) Effects of noradrenaline on miniature end-plate potentials and on end-plate potential. J Theor Biol 36:81–88. https://doi.org/10.1113/jphysiol.1971.sp009557

Legay C (2018) Congenital myasthenic syndromes with acetylcholinesterase deficiency, the pathophysiological mechanisms. Ann N Y Acad Sci 1413(1):104–110. https://doi.org/10.1111/nyas.13595

Lin J-W, Faber S (2002) Modulation of synaptic delay during synaptic plasticity. Trends Neurosci 25:449–455

Misra H, Fridovich I (1972) The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J Biol Chem 247(10):3170–3175

Oliver G, Schäfer EA (1895) The physiological effects of extracts of the suprarenal capsules. J Physiol 18(3):230–276

Palop G, Romero AM, Calatayud JM (2002) Oxidation of adrenaline and noradrenaline by solved molecular oxygen in a FIA assembly. J Pharmaceut Biomed 27(6):1017–1025. https://doi.org/10.1016/S0731-7085(01)00610-0

Rodrigues A, Messi M, Wang Z-M, Abba M, Pereyra A, Birbrair A, Zhang T, O'Meara M et al (2019a) The sympathetic nervous system regulates skeletal muscle motor innervation and ACh receptor stability. Acta Physiol 225:e13195. https://doi.org/10.1111/apha.13195

Rodrigues A, Wang Z-M, Messi M, Delbono O (2019b) Sympathomimetics regulate neuromuscular junction transmission through TRPV1, P/Q- and N-type Ca^{2+} channels. Mol and Cell Neurosci 95:59–70

Rudolf R, Khan MM, Lustrino D, Labeit S, Kettelhut IC, Navegantes LC (2013) Alterations of cAMP dependent signaling in dystrophic skeletal muscle. Front Physiol 4:290. https://doi.org/10.3389/fphys.2013.00290

Schneggenburger R, Neher E (2000) Intracellular calcium dependence of transmitter release rates at a fast central synapse. Nature 406(6798):889–893

Schneggenburger R, Neher E (2005) Presynaptic calcium and control of vesicle fusion. Curr Opin Neurobiol 15(3):266–274

Soić-Vranić T, Bobinac D, Bajek S, Jerković R, Malnar-Dragojević D, Nikolić M (2005) Effect of salbutamol on innervated and denervated rat soleus muscle. Braz J Med Biol Res 38(12):1799–1805. https://doi.org/10.1590/S0100-879X2005001200008

Straka T, Vita V, Prokshi K, Hörner SJ, Khan MM, Pirazzini M, Williams MPI, Hafner M et al (2018) Postnatal development and distribution of sympathetic innervation in mouse skeletal muscle. Int J Mol Sci 19(7):1935. https://doi.org/10.3390/ijms19071935

Tsentsevitsky AN, Kovyazina IV, Bukharaeva EA, Nikolsky EE (2018) Effect of noradrenaline on the kinetics of evoked acetylcholine secretion in mouse neuromuscular junction. Biochemistry A 12:327–332. https://doi.org/10.1134/S1990747818070012

Tsentsevitsky AN, Khuzakhmetova VF, Bukharaeva EA (2019a) Adrenergic modulation of excitation propagation in peripheral synapses. Biochemistry A 13(3):187–193. https://doi.org/10.1134/S1990747819030097

Tsentsevitsky AN, Kovyazina IV, Bukharaeva EA (2019b) Diverse effects of noradrenaline and adrenaline on the quantal secretion of acetylcholine at the mouse neuromuscular junction. Neuroscience 423:162–171. https://doi.org/10.1016/j.neuroscience.2019.10.049