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REVIEWS

Synchronous and Asynchronous Quantal Release at Synapses

E. A. Bukharaeva[a, b]

[a] *Kazan Institute of Biochemistry and Biophysics, Russian Academy of Sciences, P.O. Box 30, Kazan, 420111 Russia*

[b] *Kazan Federal University, ul. Kremlevskaya 18, Kazan, 420008 Russia*

e-mail: elbukhara@gmail.com

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Abstract—According to the modern conceptions of the processes of synaptic transmission of excitation there are two forms of quantal neurotransmitter release evoked by the neural stimulus – phasic synchronous and delayed asynchronous release differentiated by the intensity and temporal parameters of quanta secretion. This review is dedicated to the analysis of temporal characteristics of evoked synchronous and delayed asynchronous release of neurotransmitter quanta at chemical synapses. The data indicative of different mechanisms of realization and modulation of these types of the evoked quantal secretion are discussed. The importance of temporal parameters of neuronal secretion for maintenance of effective synaptic transmission of excitation and alteration of these parameters in some pathologies is considered.

Keywords: synaptic transmission, kinetics of secretion of neurotransmitter quanta, phasic synchronous and delayed asynchronous quantal release

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INTRODUCTION

The main structure unit that maintains intercellular transduction of information in nervous system is a chemical synapse. Basic principles of functioning of such synapses in the central and peripheral nervous system are similar [1]. In response to a nerve impulse, after a short time interval called "a synaptic delay", from presynaptic endings a release of neurotransmitter quanta occurs, the number of which varies from a few to several hundreds. These quanta generate postsynaptic responses by interacting with receptors on the effector cell membrane [2, 3]. According to the modern view, there are two forms of the stimulation-evoked quantal neurotransmitter secretion: phasic synchronous and delayed asynchronous release, which differ in the intensity and degree of the quanta secretion synchrony, as well as in their mechanisms and the contribution to the process of the information transmission in a synapse [4]. Temporal parameters (kinetics) of the evoked neurotransmitter release and the number of the releasing quanta are the characteristics of the neuronal secretion process [5, 6]. However, the question if the kinetics changes are significant for the maintenance of the efficacy and reliability of the synapse function remains disputable. In this review, the features of phasic synchronous and delayed asynchronous quantal release are considered, as well as a functional role of different forms of secretion in chemical synapses.

TIME COURSE OF THE EVOKED SECRETION OF THE NEUROTRANSMITTER QUANTA

The process of quantal release starts not earlier than 0.2–0.5 ms after the peak of the endplate action potential. This interval is specified as a minimal synaptic delay. A duration of this delay shows the time required for the release of the fastest neurotransmitter quanta, e.g., the quanta that are most ready to release [7]. When the quantal secretion occurs in the synapses where the probability of release is reduced, it is possible to record the moments of the release of separate quanta by measuring their real synaptic delays that represent the intervals between the peak of the sodium component of the endplate action current and the beginning of the postsynaptic response (Fig. 1, panel (a) and *insert* therein). The release of individual quanta of the mediator from the nerve terminal under the conditions of a reduced probability of secretion and in the case of the multiquantal response proceeds with various synaptic delays [7, 8].

To describe quantitatively the kinetics of quantal secretion, distribution histograms of real synaptic delays of uniquantal postsynaptic responses evoked by multiple stimulation of the nerve ending are analyzed (Fig. 1, panel (a)) [7, 9]. To determine temporal parameters of the secretion of quanta forming multiquantal signals, special mathematic methods are applied that make it possible to estimate the distribution of the moments of the release of each quantum comprising these responses [10–12].

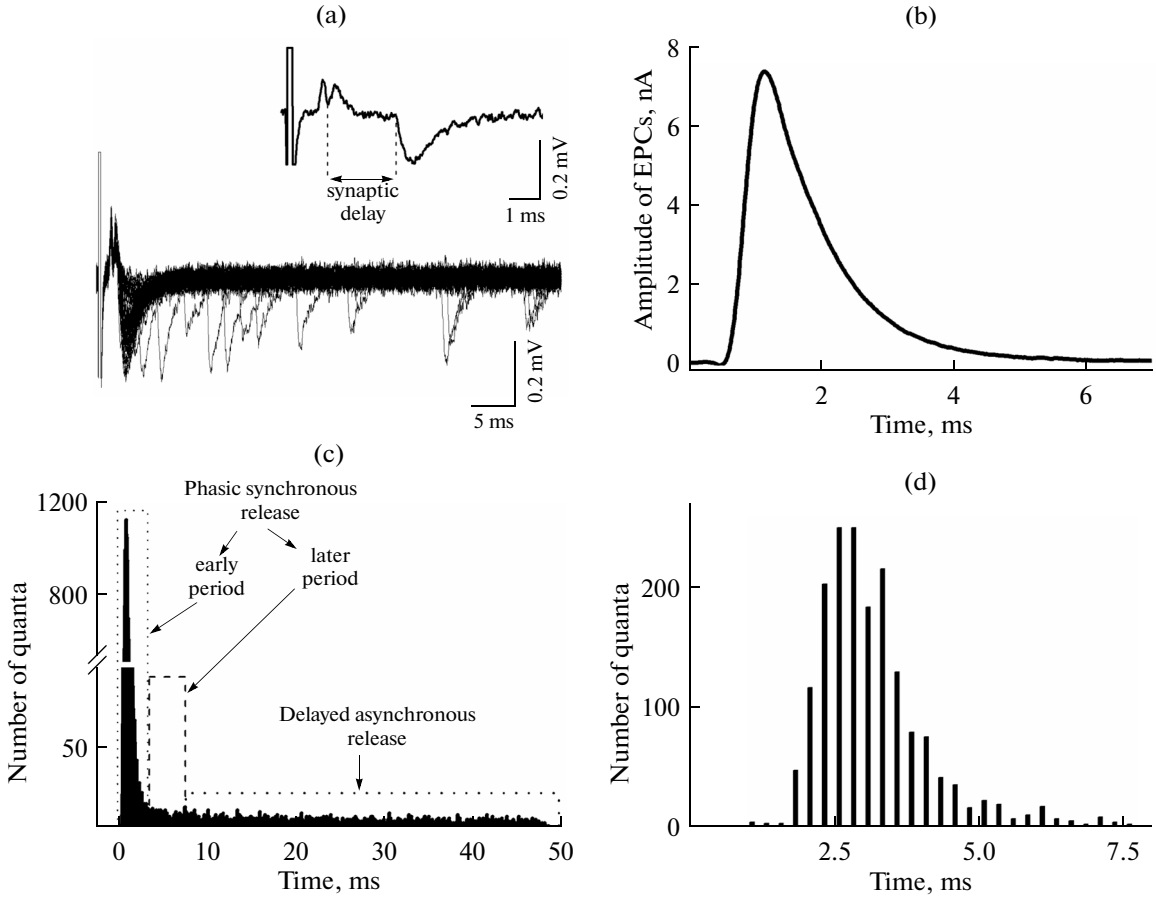

Fig. 1. Phasic synchronous and delayed asynchronous release of quanta in response of the nerve stimulus. (a) Fluctuations of real synaptic delays of uniquantal endplate currents extracellularly recorded in a distinct region of mice synaptic contact in a decreased probability of secretion and in a low calcium concentration of extracellular solution. A superposition of 50 randomly selected signals. In insertion – one of the recorded signals with indication of synaptic delay – a time interval between a peak of the sodium current component of the nerve ending action and a beginning of the postsynaptic response. (b) Histogram of the real synaptic delays distribution of uniquantal endplate currents, a part of these is represented on panel (a). (c) Multiquantal endplate current recorded by the voltage-clamp method in a frog synapses at the full quantum content. (d) Histogram of the distribution of moments of quanta releasing forming a full-quantal response represented in on panel (c). Histogram was obtained by the sequential subtraction method.

Synaptic delay is associated exclusively with presynaptic events and is determined by the time required for the maintenance of the electro-secretory coupling. These processes involve the opening of voltage-depending calcium channels, formation of nano- and microdomains of the increased calcium concentration in the active zone of secretion responsible for neurotransmitter exocytosis [4, 7, 8]. Besides, the time required for the interaction between proteins of the presynaptic membrane and proteins of synaptic vesicles in the secretion site, as well as the time of the pore opening, through which the transmitter enters the synaptic cleft from the vesicle, also contributes to the duration of the synaptic delay [4, 7, 13].

Based on the analysis of the time intervals of releasing of neurotransmitter quanta, two components of secretion are distinguished: phasic synchronous and delayed asynchronous release (Fig. 1, panel (b)) [4, 9, 14, 15]. Phasic quantal release (with slight fluctuations of the secretion moments) endures just a few milliseconds; during the following tens of milliseconds, quanta with significantly varying synaptic delays are observed, which represent the delayed asynchronous release (Fig. 1, panels (a, b)).

FEATURES OF PHASIC SYNCHRONOUS NEUROTRANSMITTER RELEASE

Although the phasic quanta secretion is called synchronous, the analysis of the moments of the quantum release shows that in the neuromuscular junctions of cold-blooded animals the release of several dozens or hundreds of neurotransmitter quanta does not occur exactly at the same time [16, 17]. Non-synchrony of the neurotransmitter release, reflected in fluctuations of the synaptic delay values, is particularly apparent at

low temperature or other conditions lowering the probability of the quantal secretion [7, 9, 18].

Phasic synchronous release of the quanta is determined by the short-term increase of the calcium concentration up to 10–100 μM in the area of the nano- and microdomains forming near the voltage-dependent calcium channels [19, 20] and also by the interaction between calcium ions and low-affinity sensor. The most relevant candidates for this role are synaptic proteins synaptotagmine I and synaptotagmine II [21, 22]. The synchronous quantal release requires the binding of calcium ions with synaptotagmine, complexine, and RIM proteins to provide a closer interaction of the synaptic vesicles and voltage-dependent calcium channels [23, 24].

Non-synchrony is inherent not only to the separate neurotransmitter quanta but also to the quanta forming a full-scale multiquantal response [16, 25]. By using mathematical methods of the multiquantal postsynaptic response analysis [10, 11], including a method of "sequential subtraction" developed by our laboratory [12], we showed that quanta forming the multiquantal response (Fig. 1, panels (c, d)) also exhibit a clear dispersion of their delays [12, 16, 25].

Not only for uniquantal but also for multiquantal responses, the time interval could be divided into two periods. The first one is an early period of phasic synchronous secretion beginning after the minimal synaptic delay. This period is characterized by the release of most of the quanta with similar delays that determine the value of the main mode in the distribution histogram of synaptic delays [7, 9, 25, 26]. The second, later period of the phasic secretion is formed by the quanta releasing with more fluctuating delays exceeding the main mode of the histogram in a range of a few milliseconds. These quanta can participate in the formation of the phasic multiquantal postsynaptic response [16, 25, 26].

The analysis of the distribution of the synaptic delays of uniquantal currents in the mouse neuromuscular synapse performed by the Bayess statistical method showed that this distribution is fitted as an exponentially modified normal distribution [27]. The presence of normal and exponential components in this distribution indicates that this is a two-stage process, involving early and late periods of the phasic synchronous release. Furthermore, the model experiments show that quanta released at the late phase of secretion can participate in a formation of the multiquantal postsynaptic response [28].

Our studies showed that the temporal parameters (minimal synaptic delay, a value of the main mode of the synaptic delay distribution, a degree of fluctuations of delays of the quanta forming the early and the late secretion periods) of the phasic synchronous secretion depend on the frequency of the motor nerve stimulation [29], calcium entry during the development of the action potential-evoked depolarization of the nerve ending (e.g., alterations of the calcium concentration in the solution, partial blockade of the potential-dependent calcium channels, increase of the calcium entry into the terminal combined with potassium channels blockade) [26] and also on the activity of the intracellular calcium buffer system [30]. A high degree of the nonsynchrony of the phasic secretion, especially of its late period, is clearly pronounced in animal synapses at early periods of the postnatal development [31]. Different types of presynaptic receptors are involved in the modulation of the secretion kinetics; activation of these receptors increase or decreases the degree of synchrony of the phasic quantal release of acetylcholine in neuromuscular synapses [18, 32–34].

It is noteworthy that the kinetics of phasic secretion differs in mouse and frog neuromuscular junctions that have a number of remarkable distinctions in morphology. Our results show that elongated nerve terminals at the frog's synapses with considerable branching [35] have temporal parameters differing even within the same terminal, suggesting the existence of the proximal-distal gradient of the secretion kinetics [36, 37]. A decrease in the rate of the excitation transduction along the nonmyelized site of the terminal significantly contribute to the non-synchrony of the phasic secretion [29]. Compact organization of mouse neuromuscular junctions, differing from the frog synapses by the structure of the active zone, demonstrate a more pronounced dependence of the phasic synchronous release on the intracellular calcium concentration [26, 37, 38].

Non-synchrony of the evoked quantal release is described not only for the peripheral neuromuscular synapses [7, 9, 16, 18, 29–38] but also for the central nervous system [39, 40]. Thus, in cultured hippocampal neurons the release of distinct quanta occurs with a clear dispersion of synaptic delays [41]. Distribution of these delays exhibits a biphasic decay, suggesting the existence of an early and late periods of secretion [42]. Heterogeneity of the secretion probability is revealed in particular in a big excitatory synapses of calux [43, 44], synaptic junctions of the vestibulo-cochlear nerve, and anteroventricular neurons of the cochlea [45]. Moreover, it was shown that synapses formed by one pyramidal neuron and several interneurons have different characteristics of the secretion kinetics [46].

During the phasic secretion, the amplitude and temporal parameters of the multiquantal response significantly change, depending on the degree of the non-synchrony of the individual quanta release [25, 28, 33]. An increase in the secretion non-synchrony leads to an increase of the postsynaptic response duration and a reducion of its amplitude [29, 32]. It should be mentioned that amplitude and temporal parameters of the postsynaptic current and potential differ due to the influence of the passive electrical properties of the postsynaptic membrane (its resistance and capacitance) on the postsynaptic potential. Experimental and modeling studies demonstrate that the parameters of the postsynaptic membrane currents

undergo more prominent changes that are dependent on the degree of the secretion non-synchrony; however, the amplitude and the time of the potential rise and decay change as well [25, 28, 35]. It is reasonable to suppose that in some cases, when the resistance of postsynaptic membrane changes along with the secretion kinetics (increase in the muscle fiber diameter in the nerve–muscle junction, partial blockade of the receptors, etc.), the non-synchronous quantal release could lead to the formation of the postsynaptic potential that does not reach the critical depolarization level, sufficient for the generation of the postsynaptic action potential [47]. This is of fundamental importance for the maintenance of the synaptic transmission reliability, since it is the amplitude-temporal parameters of the response that account for the emergence of the action potential in the postsynaptic cell [2, 3, 5, 28].

Changes of the time course of the phasic secretion occur in a number of pathological states. For example, in the case of spinal muscular atrophy characterized by the weakness of the body and limbs muscles, the amplitude of the postsynaptic response is decreased by 50%, while the rise time is more than twofold increased, and all this is due to the enhanced non-synchrony of the release of acetylcholine quanta [48]. It was established that the development of schizophrenia is accompanied by the dysfunction of gene *DTNBP1* encoding protein dysbindine. Reduction of the dysbindine expression leads to a desynchronization of the neurotransmitter secretion that results in a decrease of the amplitude of the postsynaptic response and increase of its duration [49]. A high degree of the non-synchrony of the mediator secretion is observed in patients with a hemiplegic migraine, which is accompanied by mutations of the P/Q type calcium channels and is manifested as a muscle weakness [50]. These data suggest that a search for the ways of selective influence on the temporal parameters of the phasic synchronous quantal release can help in designing of new therapeutic agents against the dysfunctions of neurosecretion processes in synaptic contacts.

DELAYED ASYNCHRONOUS RELEASE OF THE NEUROTRANSMITTER QUANTA

A distinctive feature of the delayed asynchronous release is that it lasts a few tens of milliseconds after the termination of the presynaptic action potential (Figure, panel (b)), and the quanta forming this type of secretion are not involved in the phasic multiquantal response [14, 51, 52]. In many central and peripheral synapses delayed asynchronous release is most pronounced during the high-frequency stimulation of the nerve ending [14, 15, 53, 54]. However, in a number of specialized synapses of CNS, such as cholecystokinine-containing interneurons, glutamatergic synapses of the hypothalamus cells, synapses of the dorsal horn and cerebellum, the delayed asynchronous release is also observed at a low-frequency stimulation and can be a predominant type of the neurotransmitter secretion [55–57].

The delayed asynchronous release is much less investigated than the phasic one but may constitute a major part of the secretory process in some pathological [58, 59] or special physiological states of the synaptic apparatus characterized by a low probability of the quantal release, for example, in a newly formed synapses or in the synapses of animals at early stages of postnatal ontogenesis [15, 31, 60, 61]. A phasic secretion of neurotransmitter quanta and delayed asynchronous release are controlled by different mechanisms whose nature is still not clarified [62–64]. Differently directed changes in phasic and delayed asynchronous release were described: when the phasic secretion level decreases, the intensity of the asynchronous delayed release of neurotransmitter quanta increases [65–67].

It was shown that at physiological calcium concentrations in the CNS synapses and in the neuromuscular junction of a freshwater fish Danio, a depression of phasic synchronous secretion induced by a rhythmic stimulation of presynaptic nerve ending is accompanied by an increase of the delayed asynchronous secretion of neurotransmitter [64, 65, 68].

According to one of the hypotheses, the delayed asynchronous release is related with the accumulation of the so called "residual" calcium, which cannot be sequestered by the calcium buffer systems within time intervals between the nerve stimuli, as this component of the secretion is traditionally studied in the conditions of high-frequent rhythmic stimulation of the nerve ending [15, 68].

Our investigations showed that in neuromuscular synapse of mouse and rat the delayed asynchronous release is manifested at a low probability of secretion (a decreased level of extracellular calcium) and at a low frequency of stimulation (0.5 impulses/s). A contribution of the phasic and delayed asynchronous secretion into a total number of the released quanta depends on the state of the intracellular calcium metabolism and changes differently upon variations of the calcium entry from the extracellular space [67]. A decrease of the calcium extracellular concentration leads to a sharp decline of the number of quanta released within an early period of the phasic secretion, owing to an insufficient activation of the low-affinity calcium sensor triggering the synchronous release of quanta. Similar effect is caused by magnesium- or cadmium-induced blockade of the calcium entry through voltage-dependent calcium channels. At the same time, the amount of quanta released during the period of the delayed asynchronous secretion increases under these conditions, suggesting differences in the mechanisms of modulation of these types of secretion [67].

It is noteworthy that in contrast to mature animals, in the neuromuscular synapses of newborn animals the delayed asynchronous quantal release is much more

pronounced than the phasic synchronous release [31]. Moreover, in synapses of newborn aminals the intensity of the delayed asynchronous release depends on the activity of dihydropyridine-sensitive voltage-dependent calcium channels, while in mature animals it changes upon blockade of ryanodine receptors [31].

In contrast to the phasic secretion, asynchronous release of vesicles does not require synaptotagmin I or II as a calcium sensor, while complexines limit its intensity [4]. However, realization of the asynchronous secretion requires an activation of dynamine and protein DOC2 [4, 24, 62]. Isoforms of synaptotagmin V, VI, VII, IX, and X, having a slow or intermediate kinetics of calcium interaction in comparison with synaptotagmin I, can be the sensors of the delayed asynchronous release of neurotransmitter quanta. The intensity of both synchronous and asynchronous quantal release is decreased by a fast chelator of calcium ions (BAPTA-AM); this suggests rather a close co-localization of the calcium channels providing Ca^{2+} entry and the sensors interacting with this calcium [4, 66, 67].

A physiological role of the delayed asynchronous quantal release for synaptic function still remains uncertain. It was shown that in CNS synapses the delayed asynchronous release of quanta provides an additional depolarization of postsynaptic cell that improves the synaptic transmission of the excitation [69]. The asynchronous release in autotopic synapses between fast-spiking neuron and pyramidal neuron also controls the excitability of the former and thus increases the activity of the neural network [60]. Thus, the emerging delayed asynchronous responses can facilitate the formation of the neural networks required for the development of cognitive functions [4, 66, 70, 71]. It cannot be excluded that in the peripheral neuromuscular synapses, especially in the conditions of the decreased intensity of the phasic synchronous release of quanta (in some pathologies and in developing synapses), asynchronous delayed release can participate in the maintenance of the effective synaptic transduction of excitation.

In some of pathologies, the intensity of the delayed asynchronous release of neurotransmitter quanta increases. For example, an increase of the activity of the beta-amyloid precursor associated with the Alzheimer's disease strengthens the depression of postsynaptic responses in the neuromuscular synapse and intensifies the asynchronous release [58]. In the neuromuscular synapses of animals with model spinal muscular atrophy an increase of the delayed asynchronous release up to 300% was described [59].

The analysis of the data obtained on central synapses and neuromuscular peripheral synapses has shown that the temporal parameters of the quantal secretion of the neurotransmitter evoked by the nerve stimulus, are important for the synaptic transmission and can change considerably both during ontogenesis and in pathological states.

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