Review

Synaptic Feed-backs Mediated by Potassium Ions

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Abstract. Repetitive activity of the neuromuscular system and of neuronal centers leads to K^+ efflux from excited cells and to its accumulation within extracellular spaces and synaptic clefts, especially during the generation of postsynaptic responses such as end-plate potentials or excitatory postsynaptic potentials.

K^+ ions accumulated within the synaptic cleft during activity modulate the transmitter secretion from motor nerve terminals. Depending on the concentration, K^+ can either increase the transmitter release due to a specific presynaptic action or decrease it due to depolarization of the presynaptic membrane. The dual antidromic action of K^+ can be the basis of functional self-regulation of the synapse.

The significance of the positive presynaptic action of K^+ can be assumed to enhance the reliability of the synaptic transmission at moderate activation rates. The negative presynaptic action of K^+, which predominates at high-frequency activities or during neuromuscular fatigue, leads to randomized failures of transmissions at individual synapses, the overall pattern of activation of the entire system being reproduced. This might save the general capability of the system and protect its weakest elements.

The positive antidromic action of K^+ can be assumed to be essential to the mechanism of heterosynaptic facilitation and long-term potentiation at learning synapses of the brain.

Key words: Potassium ions — Synapse — Antidromic action — Feedback

1. Activity-induced potassium accumulation in extracellular spaces and synaptic clefts

It is well known that generation of an action potential (AP) in nerve or muscle fibres is accompanied by an outflow of intracellular K^+ into extracellular space (Adrian et al. 1970). Release of K^+ during postsynaptic reaction to transmitter

action at neuromuscular junctions has been shown as well (Takeuchi and Takeuchi 1960).

Use of K^+-selective microelectrodes has allowed to demonstrate K^+ accumulation in extracellular spaces of exercising skeletal muscles (Hník et al. 1976). Substantial increase in external K^+ concentration ($[K^+]_0$) by 9 mmol/l has been detected near a repetitively active fibre within the muscle (Hník et al. 1976), and slight increase (by 2 mmol/l) in $[K^+]_0$ has been measured near a repetitively active single motor nerve ending (Smith 1982). Activity-induced increases in $[K^+]_0$ have been demonstrated also by non-invasive methods in effluent venous blood from muscle (Hník et al. 1976) and in incubation medium at the muscle surface (Kubasov 1990; for a review, see Matyushkin 1980).

Undoubtedly, the steady-state K^+ accumulation in extracellular spaces of repetitively active muscle must lead to an elevation of $[K^+]_0$ within synaptic clefts of neuromuscular junctions. An additional K^+ excess should appear in synaptic clefts during generation of postsynaptic end-plate potentials (EPP) and, to less extent, of presynaptic AP.

K^+ accumulation in synaptic clefts of neuromuscular synapses as a result of the EPP generation has been evidenced in our experiments on frog cutaneous-pectoris muscle, with muscle AP abolished (Matyushkin et al. 1978, 1984). It was shown that an increase in the nerve stimulation frequency from 1 to 50 s^{-1} produced significant shifts of reversal potentials of EPP or end-plate currents (EPC) towards more positive membrane potentials. According to calculations, the increase in $[K^+]_0$ in the synaptic cleft from 2 to 5–7 mmol/l can be expected to underlie the observed positive shifts of the reversal potentials (Matyushkin et al. 1984).

Indirect evidence has been obtained that repetitive synaptic activity at relatively low frequencies (3–4 s^{-1}) also produces slight K^+ accumulation in the synaptic clefts of the neuromuscular junctions (Matyushkin 1980, 1989). The latter result is consistent with the concept of restricted diffusional exchange of K^+ between synaptic cleft and extracellular space (Takeuchi and Takeuchi 1961).

The cause of the retarded K^+ diffusion in this case is probably reversible K^+ binding to cell glycocalix and to glycosaminoglycans of the extracellular matrix (Rice et al. 1985; Krivoi et al. 1987; Matyushkin 1989). As a result, the fraction of free K^+ can be expected to be diminished which is supposed to slow down the diffusional lost of K^+ from the synaptic cleft. On the other hand, the fraction of reversibly bound K^+ may contribute to replenishment of depleted free K^+ fraction. These processes in combination should provide relatively slow K^+ efflux from the synaptic cleft. A model of restricted diffusion was comprehensively developed for acetylcholine at neuromuscular synapse (Katz and Miledi 1973). A model for K^+ has been discussed in one of our previous studies (Krivoi et al. 1987).

Extracellular K^+ accumulation in the brain and the spinal cord was reported by a number of authors (for a review, see Matyushkin 1980). Marked accumulation

of K^+ in the synaptic cleft resulting from postsynaptic activity has been found at the squid giant synapse (Erulkar and Weight 1977).

Thus, repetitive activity of the neuromuscular system is accompanied by substantial accumulation of potassium ions within synaptic clefts of active synapses mainly due to postsynaptic processes, i. e., EPP and muscle AP. Similar phenomena can occur at chemical excitatory synapses in central and peripheral nervous system (Erulkar and Weight 1977).

2. Presynaptic effects of potassium ions

It has long been shown that upon an elevation of $[K^+]_0$ the frequency of spontaneous miniature end-plate potentials (MEPP) increases due to depolarization of motor nerve terminal (Katz 1962). Nerve terminal depolarization can result in a decrease in the amplitude of presynaptic AP and hence, in the EPP quantal content (Takeuchi and Takeuchi 1961). Under special conditions, e.g., with acetylcholinesterase inhibited, the presynaptic depolarization can even excite the motor nerve terminal eliciting antidromic AP (Katz 1962; Hohlfeld et al. 1981).

Sometimes however the elevation of $[K^+]_0$ can increase the EPP quantal content (Takeuchi and Takeuchi 1961). Such a positive presynaptic effect of moderately elevated $[K^+]_0$ (from 5 to 15 mmol/l), shown by Parsons et al. (1965) at synapses of the rat diaphragm, was manifested both in Mg^{2+}-blocked preparations (with lowered EPP quantal content), and at curarized ones (with intact EPP quantal content). The actions of K^+ in these two cases were equal in magnitude. The authors also mentioned that a three-fold elevation of $[K^+]_0$ reduced the rate of the EPP run-down observed during repetitive trains. They have suggested that K^+ ions exert a positive action both on quantum release probability and on available transmitter stores.

We have performed independently similar experiments with synapses of frog cutaneous-pectoris muscle (Matyushkin et al. 1978; Matyushkin 1980), and have found that even a relatively slight $[K^+]_0$ elevation (from 2 to 4.7 mmol/l) led to dramatic increase in the EPP quantal content (by 155%). At 8.7 mmol/l K^+, the quantal content was on average raised by 273%, and sometimes even by 500%. Higher K^+ concentrations resulted, however, in a decrease (at 15.4 mmol/l) or blockade (at 24 mmol/l) of EPP.

Thus dual presynaptic effect of potassium ions depending on their concentration has been revealed. In fact, we are dealing with two presynaptic actions of K^+ ions: positive and negative. The two actions can be expected to sum up algebraically, the negative one being enhanced as K^+ concentration increases.

In our experiments with frog synapses, like in the above mentioned experiments of Parsons et al. (1965) with mammalian synapses, the magnitude of the positive presynaptic K^+ action did not strongly depend on the EPP quantal content

(Matyushkin et al. 1978; Matyushkin 1980). At the same time at low stimulation frequencies (3–4 s^{-1}) the magnitude of the described positive effect of K^+ used in concentration 8.7 mmol/l, was found to be the lower, the higher the initial EPP amplitude. This can be explained by a release of larger amounts of K^+ ions during the generation of high-amplitude EPP. Such a K^+ surplus within the synaptic cleft (calculated to be about 2.5 mmol/l), adds up to K^+ ions which have entered into the cleft from the external hyper-potassium solution. Thus, the resulting K^+ concentration in the synaptic cleft may reach a level provoking depolarizing presynaptic action thereby masking the positive K^+ effect. Perhaps, this explains the absence of reports about any substantial positive presynaptic K^+ effect in studies performed in conditions preserving the generation of high-amplitude EPP (Dobretsov 1987).

The positive action of elevated $[K^+]_0$ on the EPP quantal content has been shown to be mainly due to an increase in quantum release probability, i. e., in binomial parameter p (Matyushkin 1980).

What is the essence of this effect? In study of positive action of hyper-potassium solutions on the MEPP frequency, Cooke and Quastel (1973) have found out that there was a specific, rapid component of this action unrelated to K^+-induced depolarization of presynaptic membrane but probably related to an increase in voltage sensitivity of its Ca^{2+} channels (this effect was counteracted by an excess of external Ca^{2+}).

It can be assumed that similar specific K^+ effect could underlie the positive K^+ action on evoked transmitter release as well (Matyushkin et al. 1978; Matyushkin 1980, 1989). However another explanation of the latter effect is likely (Robitaille and Charlton 1992). $[K^+]_0$ elevation is known to reduce the repolarizing K^+ current of excited nerve terminal, thus leading to a broadening of the presynaptic AP. This in turn results in an increase in evoked quanta release. We shall term this mechanism of increase in EPP quantal content as non-specific, or "gradiental".

In experiments with simultaneous extracellular recording of EPC and nerve terminal action currents in frog skeletal muscle, we have shown that the increase in the EPC quantal content, produced by 8 mmol/l of K^+ did not correlate with K^+-induced alterations in amplitudes or time courses of the main phases of presynaptic action current. This allowed to suppose that a modification of the amplitude or of the duration of presynaptic AP due to the "gradiental" K^+ action was not the main cause of the observed dramatic positive effect on the evoked transmitter release (Dobretsov et al. 1987).

It can be suggested that a Ca^{2+}-dependent K^+ current (which also depends on K^+ gradient) could play a role in the quantal content increase. This small current component might be missing in our measurements of parameters of the nerve terminal action currents. However, it was shown (Robitaille and Charlton 1992) that even complete blockade of Ca^{2+}-dependent K^+ channels of motor nerve terminal with specific antagonists resulted in a maximum two-fold increase in evoked

transmitter release, whereas 3- to 6-fold increases in EPP quantal contents were obtained in hyper-potassium solutions (Matyushkin et al. 1978; Dobretsov et al. 1987).

Thus, besides the described slight "gradiental" effect, a potent specific action of K^+ postulated by Cooke and Quastel (1973) for the K^+-induced stimulation of spontaneous quantal release, can be expected to be also involved in the observed stimulation of evoked transmitter release.

The mechanism of the specific presynaptic K^+ action remains unknown. The suggestion that it might be related to the activation of membrane Na^+, K^+ ATPase, can be rejected as ouabain, a specific inhibitor of this enzyme, does not block but rather increases the MEPP frequency and the EPP quantal content (e.g., Matyushkin 1989). Most probably, external K^+ affects presynaptic voltage-dependent Ca^{2+} channels, as proposed by Cooke and Quastel (1973).

Some experimental observations obtained in our laboratory suggest that the positive K^+ action on the EPP quantal content develops rapidly: it can be revealed as early as 20 ms after a transient $[K^+]_0$ increase in the synaptic cleft (Matyushkin et al. 1984; Krivoi et al. 1987; in more detail, see section 3). On the other hand, the increase in the EPP quantal content, produced by an application of hyper-potassium (8 mmol/l) solution, continued to rise for at least ten minutes after $[K^+]_0$ (measured by a K^+-selective electrode just near the surface of the recorded muscle fibre) had reached a steady-state level (see Matyushkin 1989; Kubasov 1990).

It can be speculated that the fast component of K^+ action might result from a direct influence of K^+ ions on some molecular structures of Ca^{2+} channel, resulting in a conformational change, and in a consequent increase in the probability of the channel opening in response to depolarization.

The delayed, longer-lasting component of K^+ action might be related to some secondary K^+-induced processes, possibly involving second messengers (including enhanced Ca^{2+} influx). Indeed, a number of findings allow to suggest a possible link between elevated external K^+ and activation of second messenger systems. An excess of external K^+ has been shown to promote the rise of the MEPP frequency, produced by dibutyryl-cAMP (Miyamoto and Breckenridge 1974), and to potentiate similar action of phorbol ester, an activator of protein kinase C (Scornik et al. 1990). (The latter action of K^+ seemed to be exerted beyond the step of Ca^{2+} entry into the nerve terminal, and was suggested to be caused by K^+-induced translocation of protein kinase C molecules from intracellular, i. e. inactive fraction to the membrane). K^+ was shown to enhance the polypeptide phosphorylation by endogenous protein kinases in membrane fragments obtained from cholinergic electroplax of Torpedo (Saitoh and Changeux 1980). Interestingly, high $[K^+]_0$ produced a redistribution of sites of synaptic vesicle exocytosis in the motor nerve terminal via stimulation of exocytosis from ectopic release sites (Ceccarelli et al. 1988).

If excess of external K^+ actually activates both Ca^{2+} entry into the nerve terminal and the system of second messengers, these processes might be involved also in the activation of mechanisms responsible for the formation of available quanta stores (i.e. synaptic vesicles filling and their transport to synaptic release sites), as well as in new release sites formation (Ceccarelli et al. 1988).

It can not be ruled out that synaptic Schwann cells may contribute to the processes under consideration (see reviews: Matyushkin 1980, 1989).

Needless to say, the hypothesis concerning the mechanism of the specific K^+ action on evoked transmitter release invites further investigation and verification.

It is well to bear in mind that the negative, depolarizing action of the excess of external K^+ can also be accompanied by specific chemical processes. As an example, an influx of large amounts of Ca^{2+} into the nerve terminal during its long-term K^+ depolarization can result in an activation of Ca^{2+}-dependent neutral proteases degrading cytoskeleton elements (Vrbova et al. 1988). This effect was assumed to be more pronounced in small (so-called "additional") motor nerve terminals of developing neuromuscular junctions of the rat, where more Ca^{2+} is assumed to be accumulated due to larger surface-to-volume ratio. This was suggested to be indeed the cause of complete elimination of these small neuromuscular synapses in early development when sustained muscle activity is assumed to induce permanent K^+ accumulation within extracellular clefts (Vrbova et al. 1988).

3. Contribution of the potassium component of postsynaptic current to modulation of presynaptic activity

As mentioned in section 1, EPP and muscle AP provide most of potassium ions delivery into the synaptic cleft during repetitive neuromuscular activity.

It is interesting to evaluate the functional significance of the $[K^+]_0$ increase within the synaptic cleft, brought about by the K^+ component of EPC because this component could, in principle, contribute to the modulation of activity at a singly active synapse.

The K^+ component of EPC depends on postsynaptic membrane potential (Takeuchi and Takeuchi 1960). Resting membrane potential can be changed to any desired level by the voltage clamp method. In particular, it can be adjusted at K^+ equilibrium potential (-100 – -130 mV) which excludes the K^+ component of EPC, or at the level close to that achieved at the peak of EPP (ca. -40 mV) when the K^+ component is large.

Using this approach we have shown in experiments with the frog cutaneous-pectoris muscle (Matyushkin et al. 1984; Krivoi et al. 1987; Matyushkin 1989) that the elimination of the K^+ component of EPC with a holding potential -130 mV resulted in a substantial slowing down of tetanic potentiation of EPC ($50\ s^{-1}$) compared to control recordings performed at holding potential -80 mV (enabling

a K^+ efflux). On the contrary, the EPC tetanic potentiation at −40 mV was more rapid than in controls, especially at synapses with high initial EPC amplitudes.

The described acceleration of the EPC potentiation was reduced after partial blockade of postsynaptic acetylcholine receptors (a procedure reducing the K^+ component of EPC). On the other hand, this acceleration was increased after inhibition of Na^+, K^+-ATPase, a procedure promoting K^+ accumulation in the synaptic cleft (see Krivoi et al. 1987).

A "voltage dependency" of EPC potentiation was also suggested by results of other studies (Magleby et al. 1981), but this has escaped the attention of the authors.

Thus moderate accumulation of K^+ in the synaptic cleft during repetitive EPC (or EPP) can exert the stimulatory action on evoked transmitter release, while substantial K^+ accumulation can produce the opposite effect.

As was shown in experiments with double-pulse nerve stimulation with 20 ms interstimulus interval (Matyushkin et al. 1984), the magnitude of the facilitation of the second (testing) EPC at the holding potential −80 mV (enabling the postsynaptic K^+ release) was significantly higher than at −130 mV (i.e., in the absence of the postsynaptic K^+ efflux). Thus the positive presynaptic action of K^+ released into the synaptic cleft during the conditioning EPC developed as rapidly as within 20 ms or less (shorter intervals were not tested).

One more indirect evidence of the presynaptic action of elevated $[K^+]_0$ within the synaptic cleft was obtained in experiments with EPP superimposed on muscle fibre AP (Matyushkin 1989). AP were elicited by repetitive (50 s^{-1}) intracellular stimulation of the muscle fibre with pulses of just-suprathreshold intensity (to avoid a current spread into the nerve terminal); EPP were elicited by nerve stimulation (with the same frequency), the nerve and the muscle stimuli being timed to provide simultaneous generation of EPP and muscle AP.

When stimulation of the muscle fibre was stopped after 10 superpositions (the nerve stimulation continued), the EPP quantal content was higher by about 20% than before the combined stimulation. This facilitatory effect continued to develop reaching a maximal value about 60 ms after the offset of the muscle fiber stimulation; then, it decayed during 100–200 ms. The enhancement of the EPP quantal content in these conditions can be explained by presynaptic action of the EPC K^+ component which must be substantially increased when EPP develops on the rising phase or on the peak of muscle AP, i.e., when postsynaptic membrane potential is depolarized or even inverted, and consequently the K^+ electrochemical gradient increases. It can be assumed that during the EPP-AP superpositions the negative (depolarizing) action of K^+ dominates, whereas after the offset of muscle AP, as K^+ concentration in the synaptic cleft falls down, the positive K^+ action is revealed (unmasked), decaying with time.

What is the physiological significance of the positive action of postsynaptic K^+

current on EPP quantal content? It seems to be rather clear: this action (either specific or "gradiental") withstands the depolarizing action of K^+. This compensatory effect is manifested at activation frequencies above 0.5 s^{-1} but below ca. 50 s^{-1}, i.e., when residual K^+ exists which is, however, not enough to induce strong presynaptic depolarization. In this situation the positive antidromic (retrograde) action of K^+ enhances the reliability of synaptic transmission. At frequencies above ca. 50 s^{-1} the negative (depolarizing) action of "muscular" K^+ prevails leading to a decreased in the EPP quantal content.

It the safety factor of synaptic transmission is high (i.e., 2–3), this negative action may not lead to blockade of the transmission but only to a decrease in K^+ concentration in the synaptic cleft. However, if muscular AP are not eliminated, the neuromuscular activity at these frequencies can be expected to lead to periodic failure of transmission (transformation of the activation rate) at single synapses. But for a large body of synapses within a muscle however, the distribution of these failures among different synapses can be expected to be random. Thus repetitive activations of the entire muscle follow the frequency of the nerve signals. Such randomized presynaptic blockade can save the capability of the system due to economy in transmitter expenditure, maintenance of ionic gradients across the cells and of parameters of their microenvironment within the physiological range. (Below, we shall discuss a special aspect of this saving mechanism.)

4. Possible participation of postsynaptic potassium current in adaptation of neuromuscular synapse to fatiguing muscle exercise and in long-term potentiation at brain synapses

Fatigue, i.e., reversible reduction of muscle performance during repetitive muscle exercise (activated either neurally or directly) is a very complicated phenomenon which is not completely understood. Since the time of the classic studies of Merton (1954), it is generally accepted that the limiting factor in neuromuscular fatigue is but muscle contraction mechanism and/or excitation-contraction coupling rather than synaptic transmission (for a review, see Westerblad et al. 1991). That is why the role of synaptic mechanisms in the fatigue development was not the focus of attention of most investigators except a few (Nikolsky and Poletaev 1977; Matyushkin 1989).

It is known that intensive (fatiguing) static exercise hindering the venous outflow from the muscle is accompanied by large efflux of K^+ and by its accumulation in extracellular space (Mainwood and Lucier 1972; Hník et al. 1976; Renaud and Light 1992; also see section 1). During fatigue an additional factor promoting K^+ accumulation can become operative, namely the opening of sarcolemmal ATP-dependent K^+ channels (Ashcroft 1988), induced by a lowering of intracellular ATP concentration and of pH (Davies et al. 1992) which actually is the case in fatigued

muscle fibres (Westerblad et al. 1991).

The possibility was discussed that the raised $[K^+]_0$ near the muscle surface membrane would be sufficient for large depolarization which, in turn, would be sufficient for excitation-contraction uncoupling (Sjogaard 1986; Medbo and Sejersted 1990). But this was not confirmed by recent studies (Renaud and Light 1992). Thus, K^+ accumulation is unlikely to be the main cause of muscle fatigue.

On the other hand, the resulting extracellular K^+ concentration reaching 5–10 mmol/l during neuromuscular fatigue (Hník et al. 1976; Medbo and Sejersted 1990), seems to be sufficient to produce presynaptic actions, initially positive, and later (as K^+ concentration continues to increase) negative. In fact Validov (1948) described strengthening of contractions, produced by moderate elevation of $[K^+]_0$, in fatigued neuromuscular preparation. Recently we have observed obvious biphasic effects (first positive, then negative) of external solutions with 5 or 8 mmol/l K^+ on fatigued indirectly stimulated muscle of the frog. An important point was that these effects were lacking in directly stimulated muscle (unpublished observations).

Thus similar biphasic presynaptic action of endogenous extracellular K^+ accumulated gradually during fatigue, is quite possible. If so, the second, inhibitory phase of the K^+ action can be assumed to result in periodic failures of neuromuscular transmission in a fraction of synapses or motor units. Such antidromic blockade being randomized may not lead to cessation of contractions of the entire muscle (see preceding section). At the same time, it can have physiological significance as it protects the subsequent weakest cellular elements (excitation-contraction coupling, myofibrills) from being overloaded, thereby increasing the reliability of the system (by analogy with the limitation of motoneuron outputs by recurrent inhibition with Renshow interneurons in the spinal cord).

The antidromic action of K^+ can be assumed to play a role in heterosynaptic facilitation in muscle fibres with double or multiple innervation when the synaptic force of neighboring synapses differs substantially (see Krivoi et al. 1987). In this situation the activity of a stronger synapse would result in depolarization of the shared postsynaptic membrane. The transmitter released at the weaker synapse, when active simultaneously with the stronger one (or with a short delay), would open the transmitter-activated ion channels of already depolarized postsynaptic membrane. Hence, the K^+ efflux through these channels would be larger than in the case when the weaker synapse is active alone. This enhanced K^+ signal can facilitate the subsequent transmission at the weaker synapse (like in the situation with EPP-AP superpositions described in section 3).

Similar K^+-induced antidromic mechanism can be suggested to operate at learning synapses of the brain (Matyushkin 1989). Possible contribution of postsynaptic factors in the presynaptic component of the long-term potentiation (LTP) in hippocampus has been discussed (Stevens 1989). This component was shown to be induced by the action of an agonist on postsynaptic receptors (Davies et al.

1989). Buffering of intracellular Ca^{2+} inside the postsynaptic neuron abolished LTP (Lynch et al. 1983) suggesting a "feedback-type" of relationship between the pre- and postsynaptic components of LTP. It has been suggested that postsynaptic K^+ current plays a role in LTP (Sastry et al. 1986; Ballyk and Goh 1992), and even that the extracellular K^+ action can be a prerequirement for LTP induction (Poolos et al. 1987; Poolos and Kocsis 1990). However, a conclusive target of the K^+ action was not pointed at. It has to be noted that if the neurotransmitter glutamate acting on postsynaptic NMDA-receptors provides depolarization of a hippocampal neuron, and if the subsequent Ca^{2+} influx leads to an activation of Ca^{2+}-dependent K^+ channels inside the neuron, then the efflux of postsynaptic K^+ seems to be quite plausible. Based on the outlined considerations, it would appear reasonable that the main target of K^+ action would be located at the presynaptic level. The role of the influence of K^+ on the postsynaptic membrane or on glial cells in the LTP induction cannot be excluded either.

In the last few years particular attention of many investigators studying LTP and related phenomena has been attracted to the new "transmitters" NO* and CO which are also assumed to be possible factors of antidromic action at learning synapses (Nowicky et al. 1993; Stevens and Wang 1993). Not discarding the possibility of NO* and/or CO involvement in antidromic support of LTP (along with K^+), we have to note that these metabolites, in contrast to K^+, can be expected to much more easily penetrate into all adjacent cells and to disappear much more rapidly. It seems that these properties of NO* and CO make them inappropriate to provide local, restricted to certain synapses, and sufficiently long-term action required for synaptic learning.

It is possible that there are other factors of positive antidromic actions operating at synapses (Matyushkin 1989).

It is necessary to point out that we have considerably restricted the discussion of K^+ functions leaving aside special cases such as spreading depression in the brain, pathological K^+ paralysis and many others which are beyond the scope of the present review.

Conclusion

The data considered in this review provide evidence for delayed diffusion and substantial accumulation of K^+ in extracellular spaces including synaptic clefts during repetitive activity in neuromuscular system, as well as in neuronal centers. The primary sources of this K^+ are postsynaptic processes such as EPP (or excitatory postsynaptic potentials at neuronal synapses) and AP. The main targets of the accumulated K^+ action are presynaptic nerve endings (and, possibly glial or Schwann cells).

The presynaptic action of K^+ is biphasic: low K^+ doses producing essentially

specific effect lead to an increase in transmitter release, whereas high doses of K^+ result in reduction of the release due to nonspecific depolarization of the nerve terminal followed by a decrease in presynaptic AP amplitude.

The significance of the positive (specific) presynaptic action of K^+ can be assumed to be compensation of its negative (depolarizing) action. This might enhance the reliability of the synaptic transmission at moderate rates of activation.

The significance of the negative presynaptic action of K^+, which predominates at intensive high-frequency activities or at neuromuscular fatigue may be a decrease in the frequency of transmission at individual synapses, the overall pattern of the activation of the entire system being reproduced. This is important for saving the general capability of the system and to protect its weakest elements (such as the contractile apparatus and/or excitation-contraction coupling in the neuromuscular system) which are unable to reproduce high-frequency activations.

There are good reasons to believe that the positive antidromic action of K^+ is essential to the mechanism of heterosynaptic facilitation at synapses of polyneuronally innervated muscle end-plates, as well as to the mechanism of LTP at learning synapses of the brain.

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