Minireview

Voltage-gated potassium channels: from hyperexcitability to excitement

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Abstract The superfamily of voltage-activated potassium channels may express structurally and functionally diverse voltage-activated potassium channels in the nervous system. The roles of some voltage-activated potassium channel types, e.g. rapidly inactivating (transiently active type) channels and muscarine sensitive muscarine sensitive channels, are beginning to be understood. They may significantly influence dendritic action-potential back-propagation, signal to noise ratios in presynaptic excitability or the responsiveness of a neuron to synaptic input. Inherited disorders related to changes in excitability (episodic ataxia, epilepsy, heart arrhythmia) or to defects in sensory perception (hearing loss) have been associated with mutations in a few voltage-activated potassium channel genes. Most likely, more voltage-activated potassium channel genes will be linked to related disorders in the near future.

Key words: Voltage-activated potassium channel; Action-potential; Hyperexcitability; Hearing loss

1. Introduction

K^+ channels can catalyze the transmembraneous flow of K^+ ions driven by the electrochemical gradient. Therefore, K^+ channels may be an important determinant of cellular activities, which are correlated with changes in the membrane potential. Examples range from neural signal transduction, pacemaking and secretion to the regulation of cell volume and cell proliferation. K^+ channel activities may be regulated by different physical stimuli and/or chemical agents. They include Na^+, Ca^{2+}, Mg^{2+}, ATP, O_2, pH, pressure, membrane potential, redox potential, phosphorylation/dephosphorylation, G protein binding, interaction with cytoskeletal proteins and more [1]. Accordingly, many different K^+ channels have been characterized in pro- and eukaryotic cells by biophysical, biochemical, molecular genetic and molecular biological methods [2–4].

Structural and functional analysis has shown an evolutionarily highly conserved design for K^+ channels [4,5]. The origin of this design may be found in the two-transmembrane (2-TM) K^+ channel subunits (Fig. 1). The core of these subunits exhibits a topology which can be found in all known K^+ channel α subunits [4,5]. Two hydrophobic transmembrane segments (TM), TM1 and TM2, are connected by a linker region, a loop structure that enters and exits the lipid bilayer from the extracellular side. The loop typically contains a P-domain forming an essential part of the K^+ channel pore [6]. K^+ channel P-domains may be recognized by a K^+ channel signature sequence (e.g. TVGYGD). Apparently, assembly of four P-domains is necessary to build a functional K^+ channel pore. The TM1-P-TM2 topology was confirmed last year in a landmark paper, describing the crystal structure of a prokaryotic 2-TM K^+ channel at a resolution of 3.4 Å [7]. The results have provided unprecedented insights into the structure of a K^+ channel and its pore.

The TM1-P-TM2 motif has been instrumental for the recognition of new and novel K^+ channel subunit sequences produced in genome sequencing projects [8], e.g. the completion of the *Caenorhabditis elegans* genome sequencing project (http://nt-salkoff.wustl.edu/voltage/Table.html) has provided what is most likely a complete list of K^+ channel subunits (altogether 58), which are expressed in this small worm. The comparison of the derived *C. elegans* K^+ channel sequences has suggested that K^+ channel α subunits can be grouped into four main 'structural' classes (Fig. 1) (see also [5]). The first class encodes 2-TM subunits. The other classes encode four TM (2-TM+2-TM), six TM (2-TM+4-TM) and eight TM (2-TM+2-TM+4-TM) subunits, respectively. The structural organization and relatedness of these classes suggests that K^+ channel structures may have diversified from 2-TM subunits during evolution. The 4-TM class represents an apparent duplication of the 2-TM subunit. The 6-TM class one, in which four (five in case of BK channels) additional TMs were joined to the 2-TM subunit and the 8-TM class most likely arose from combining 2-TM and 6-TM structures. Members of the 6-TM class may encode subunits of Ca^{2+}-activated K^+ channels and/or voltage-activated K^+ (Kv) channels. I shall concentrate in this review on a discussion of the latter.

2. The Kvα subunit family is large

The superfamily of Kvα (and Kvγ[1]) subunits can be subdivided into three major families. The subfamilies have derived their name from *Drosophila* and human mutants which were instrumental in cloning and characterizing the first members of each family. The first family encodes *Shaker*-related Kvα (and Kvγ) subunits, the second one *ether-à-go-go* (*eag*)-related Kvα subunits, the third one KvLQT1 (KCNQ)-related Kvα subunits (Table 1). At present, the *Shaker*-related Kv subunits family is the largest and the KCNQ-related one the smallest. Table 1 lists the presently known mammalian (human) members of the Kvα (γ) subunit superfamily. This list of 37 Kv subunits (not counting the numerous splice variants) is

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[1] Kvγ subunits are 6-TM subunits. They do not assemble to functional homomeric Kv channels. Kvγ subunits form functional hetero-multimeric Kv channels with Kvα subunits (e.g. Kv2.1 and Kv2.2) [9].

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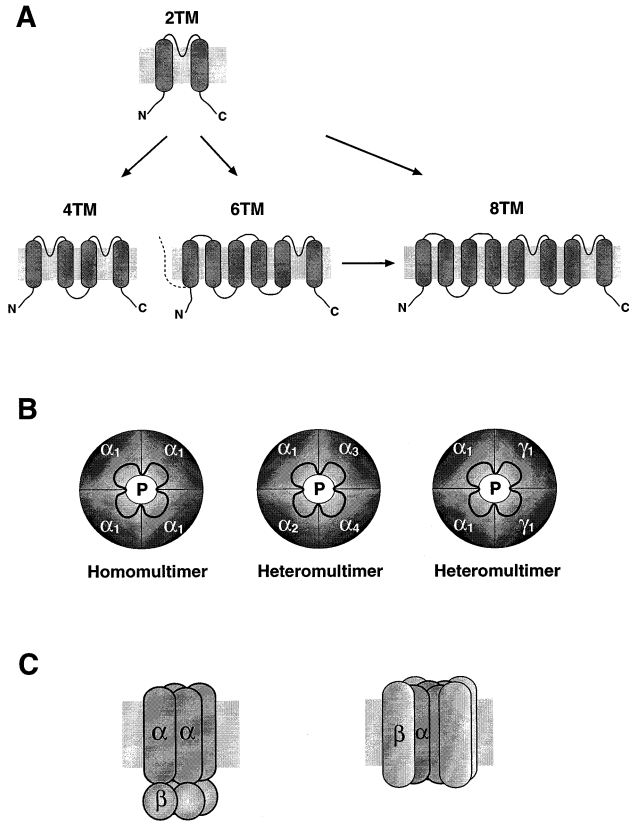

Fig. 1. A: Structural classification of potassium channel subunits. The subunits have been grouped into four main 'structure classes' encoding 2-TM, 4-TM, 6-TM and 8-TM subunits. The structures are implied from hydropathy and biochemical/molecular biological analysis except for the 2-TM subunit. In this case, the crystal structure of one 2-TM K channel has been solved. Arrows suggest how 4-TM, 6-TM and 8-TM structures may have evolved from the 2-TM structure. Kv channels belong to the 6-TM class. B: Potassium channel subunits assembly. Four P-domains may be necessary to form a functional potassium channel. Kv channels may contain homotetrameric or heterotetrameric α (γ) subunit assemblies. C: Auxiliary subunits. Kv channels may contain auxiliary β subunits, e.g. Kvβs, which are cytoplasmic proteins being bound to cytoplasmic domains of α subunits. Other β subunits (e.g. minK) may be membrane-spanning proteins interacting with cytoplasmic and/or membrane-integrated α subunit domains.

already quite extensive, but will certainly extend as the human genome project progresses further. If one takes into consideration that Kv subunits can form heteromultimers and, in addition, can assemble with various auxiliary subunits (e.g. Kvβ; minK), an impressive number of diverse Kv channels can be generated. Theoretically, it is possible that each neuron in the brain could be endowed with a distinct population of Kv channels.

3. Why so many different Kv channels?

There is no simple answer to this question, because we still do not understand enough about the role of distinct Kv channels in neuronal signalling. Some simple observations can, however, help to explain that neuronal activity requires several different Kv channels. Kv channel activity can be involved in controlling the threshold for action-potential firing, the action-potential wave form, the action-potential frequency, the burst duration of action-potentials as well as a refractory after-hyperpolarization phase (Fig. 2). The different neuronal activities most likely require Kv channels which differ in their voltage-dependence of activation and in their gating properties (e.g. time constants of activation, inactivation and deactivation). Furthermore, signal integration and action-potential 'handling' may be distinctly different in somatodendritic and axonal compartments. Probably, therefore, distinct Kv channel subunits are localized to somato-dendritic compartments, axons and presynaptic terminals [10–13].

4. Kv channels as activity-dependent shock absorbers and noise filters

For discussion, I have selected two types of Kv channels: the transiently active (A-type) Kv channels and the so-called M-channel (M for muscarine sensitive). The examples may highlight the important roles that Kv channels can play in determining the nervous excitability. Dendritic A-type channels may contain Kv4.1, Kv4.2 and/or Kv4.3 subunits [14,15]. The channels mediate voltage-activated transient outward currents, which inactivate rapidly. Recovery from inactivation takes place with time constants τ_R in the range of –100 ms. This A-type current has been recorded in somato-dendritic localizations of many neurons in rodent brain. The A-type channels apparently represent a major determinant of excitability in dendrites of CA1 pyramidal neurons, where they function as activity-dependent dendritic shock absorbers [14,16]. In the absence of an excitatory postsynaptic potential (EPSP), the A-type channel activity prevents initiation of an action-potential in the dendrites and limits the back-propagation of action-potentials (dendritic spikes) into the dendrites. In the presence of an EPSP, the depolarization of dendritic membrane inactivates the A-type channels. Thereby, a temporal coincidence of EPSP and an undampened dendritic spike

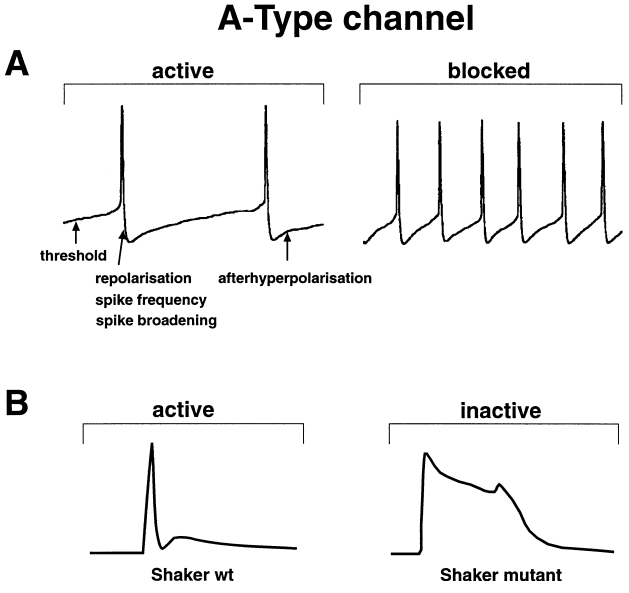

Fig. 2. Influence of A-type channel activity on the spike frequency and action-potential broadening. A: Spontaneous activity in a model neuron. Arrows indicate possible involvement of Kv channel activity in the regulation of the spiking pattern. Block of somato-dendritic Kv4.3 channels increased the spiking frequency. Data are from [39]. B: Action-potential recorded from a *Drosophila* giant fiber in wild-type (wt) and in flies (*Shaker* mutant) which do not express an axonal A-type channel. Data are from [40].

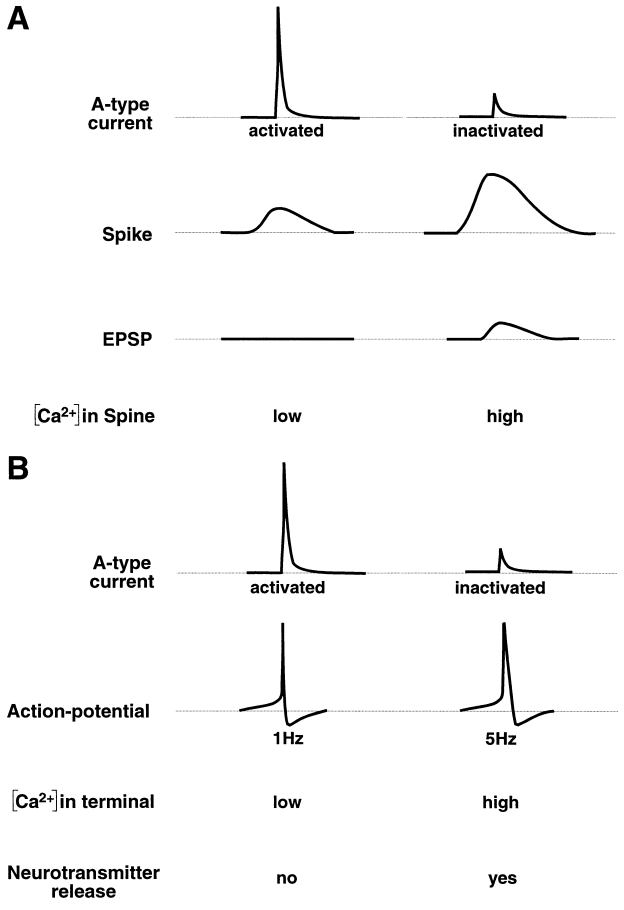

Fig. 3. Schematic illustration of possible roles of somato-dendritic and presynaptic A-type channels for Ca^{2+} influx into dendrites and into presynaptic terminals, respectively. A: Active dendritic A-type channels may efficiently repolarize back-propagating action-potentials (spikes). Temporal coincidence of EPSPs and spikes can result in a larger spike, because the A-type channels were inactivated. The elicited larger spike will generate a larger Ca^{2+} influx. For details see [14,16]. B: Active presynaptic A-type channels can repolarize action-potentials arriving at a low frequency (e.g. 1 Hz). The Ca^{2+} influx into the terminal is not sufficient to trigger neurotransmitter release. At higher frequencies of stimulation, A-type channels become inactivated. This will lead to a broadened action-potential. Now, the Ca^{2+} influx will be sufficiently large to trigger neurotransmitter release.

(Fig. 3A) are produced, which may result in a large back-propagating spike and lead to a greater influx of Ca^{2+} into the dendritic spines. Thus, the inactivation behavior of dendritic A-type channels may have an important influence in dendritic integration underlying long-term potentiation, learning and memory.

Presynaptic A-type channels apparently contain other subunits (e.g. Kv1.4, Kv3.3, Kv3.4 and/or Kvβ1 and Kvβ3) than dendritic A-type channels [10,12,13,17]. In contrast to the dendritic channels containing Kv4 subunits, these A-type channels recover slowly from inactivation in vitro (e.g. ([18]) τ_R of Kv1.4–0.5–5 s). Possibly, the slow recovery of inactivated presynaptic A-type channels is used in the presynaptic terminal to dampen action-potentials arriving at a low frequency. At higher stimulation frequencies, the A-type channels undergo a lasting inactivation [18,19]. The resulting prolonged action-potentials (as observed in some *Shaker* mutants), produce an increased Ca^{2+} influx into the terminal triggering neurotransmitter release [19]. Thereby, presynaptic A-type channels may function for synaptic output as a noise filtering device (Fig. 3B), which operates at a low frequency (below 3–10 Hz) as defined by the recovery time constant τ_R. This notion is consistent with the observation that stimulation frequencies above 10 Hz are correlated with A-type channel inactivation, action-potential broadening and neuropeptide release in pituitary terminals ([19]). Note that stimulation frequencies of –40 Hz would most likely be required for a lasting inactivation of dendritic A-type channels. It is remarkable that the pre- and postsynaptic A-type channels underlie lasting inactivations at stimulation frequencies which are conspicuously similar to the ones observed for neuronal network oscillations [20]. Neuronal networks (e.g. in the hippocampus) can produce oscillations of 4–10 Hz (theta frequency) and of 40 Hz (gamma frequency). The frequencies may be related to storage and recall of memory sequences [20]. Whether the inherent frequency sensitivity of pre- and postsynaptic A-type channel inactivation has anything to do with the generation of network oscillations is an interesting, but still very speculative hypothesis.

5. M-channels and synaptic responsiveness

M-channels mediate voltage-activated outward-currents, which practically do not inactivate and deactivate slowly [21]. The M-channel may be assembled from KCNQ2 and KCNQ3 subunits [22]. M-channel-mediated currents play a critical role in determining the subthreshold electrical excitability of neurons [23]. In the absence of agonists of muscarinic acetylcholine receptors, M-channel activity dampens the responsiveness of a neuron to synaptic input. Briefly after exposure to muscarinic agonists, M-channels are silent. This change in M-channel activity provides a mechanism for neurons to respond to excitation with a low or high sensitivity. Thus, M-channels may provide neurons with a gain-control device to favor firing a burst of spikes rather than a single spike. In conclusion, the brief discussion of the two Kv channel types may illustrate the importance of Kv channel activity in postsynaptic signal integration, in controlling signal to noise ratios in presynaptic action-potential firing and in generating bursts of spikes.

6. Phenotypes and nervous system diseases related to mutant Kv-channels

Molecular characterization of the *Drosophila* mutants *Shaker* and *ether-à-go-go* resulted in cloning the first Kv channel subunits [2–4]. The phenotypes of the mutants are inconspicuous, when raised under normal conditions in the laboratory. Under ether anesthesia, however, the mutants exhibit a strikingly abnormal leg shaking. This abnormal hyperexcitability may be correlated with an increase in action-potential firing observed in electrophysiological experiments [24]. Though *Shaker* and *eag* channels make significant contributions to the neural excitability in *Drosophila*, their loss of function apparently is not detrimental to the fly's life. For comparison, a loss of function mutation in the *C. elegans* egl-36 gene encoding a Kv3 subunit also did not exhibit a grossly evident phenotype [25]. By contrast, a gain of function mutation in the same gene leads to inhibition of enteric and egg-laying muscle contraction [25]. The observations raise the possibility

Table 1
Chromosomal localizations of members of the superfamily of Kv channels and related deseases

Subunit	Chromosome	Disease	Subunit	Chromosome	Disease
Shaker-related subfamily					
KCNA1 (Kv1.1)	12p13.32	EA	KCNC4 (Kv3.4)	1p21	
KCNA2 (Kv1.2)	1p13		KCND1 (Kv4.1)	Xp11.23	
KCNA3 (Kv1.3)	1p13.1		KCND2 (Kv4.2)	7q31	
KCNA4 (Kv1.4)	11p14.1		KCND3 (Kv4.3)	1p13.3	
KCNA5 (Kv1.5)	12p13.32		KCNG1 (Kv5.1)	2p25	
KCNA6 (Kv1.6)	12p13.32		KCNG2 (Kv6.1)	20q11.3	
KCNA7 (Kv1.7)	19q13.1		KCNG3 (Kv6.2)	18q22-23	
KCNB1 (Kv2.1)	20q13.1		KCNG4 (Kv6.3)	n.d.	
KCNB2 (Kv2.2)	n.d.		Kv7.1	n.d.	
KCNB3 (Kv2.3/8.1)	8q22.3-24.1		KCNS1 (Kv9.1)	n.d.	
KCNC1 (Kv3.1)	11p15.3		KCNS2 (Kv9.2)	8q22	
KCNC2 (Kv3.2)	19q13.4		KCNS3 (Kv9.3)	n.d.	
KCNC3 (Kv3.3)	19q13.3				
eag-related subfamily					
KCNH1 (Heag1)	1q32.1		Herg3	2q22	
Heag2	14q24.3		Helk1	17	
KCNH2 (Herg1)	7q35	LQT	Helk2	12q13	
Herg2	17q29		Helk3	n.d.	
KCNQ-related subfamily					
KCNQ1 (KvLQT1)	11p15.5	LQT/JNL	KCNQ3	8q24	BFNC
KCNQ2	20q13.3	BNFC	KCNQ4	1p34	DFNB2
Auxiliary subunits					
KCNA1B (Kvβ1)	3q26.3		KCNA3B (Kvβ3)	17p13.1	
KCNA2B (Kvβ2)	1p36.1		KCNE1 (minK)	21q22.2	LQT/JNL

The data were compiled from http://www.citi2.fr/GENATLAS/welcome.htmL.

that null mutations in Kv channel genes may be associated with only subtle phenotypes. This notion might provide an explanation why only a few of the many known human Kv channel genes have been correlated with disease phenotypes.

Comparable observations have been made with mice in which the functional expression of certain Kv channel subunits were knocked out (k.o.).The phenotypes associated with the mice null mutants were not readily apparent [26–29]. Possibly, it is not always obvious to correlate the loss of function of a certain Kv channel subunit with phenotypic changes in the neuronal excitability, signal transduction and/or behavior. Representatively for some of the k.o. mice which are under study in several laboratories, I will discuss briefly results obtained with Kvβ1.1 k.o. mice [28]. Kvβ1.1 subunits confer in vitro rapid inactivation to otherwise non-inactivating Kv channels in the Kv1 family [30]. The subunits are expressed (e.g.) in CA1 pyramidal neurons of the hippocampus and in striatal neurons. Loss of Kvβ1.1 function should be correlated with a loss of A-type channel activity. However, when A-type channels were recorded from CA1 neurons, it was found that the measurable A-type channel activity was not altered to a large extent. In fact, the differences between the recordings on neurons from k.o. mice and the ones from wild-type litter mates were subtle. Subsequently, bursts of action-potentials were analyzed. Again, the changes in action-potential wave form observed with neurons of the k.o. mice were not grossly different from the ones of wild-type littermates. However, the changes were apparently sufficient to significantly reduce the amplitude of the slow after-hyperpolarizing potential (sAHP). Collectively, the results suggest that loss of the Kvβ1.1 function shows mild effects in terms of single action-potential wave forms in pyramidal neurons of the hippocampus, but quite dramatic effects in sAHP amplitudes after firing multiple action-potentials [28]. Apparently, this is associated with changes in cognitive behavior related to hippocampal storage and recall of memories.

Mutations in three Kv channel genes (HERG, KCNQ, minK) have been associated with heart arrhythmia and in the case of KCNQ/minK also with the Jervyll-Lange-Nielsen syndrome associated with deafness [31]. Mutations in the KCNQ4 gene [32] have been correlated with a form of non-syndromic dominant progressive deafness (DFNA2). KCNQ4 is expressed in outer hair cells. The DFNA2 mutations have been detected in the KCNQ4 P-domain. This would nicely explain that DFNA2 mutant KCNQ4 channels are non-conducting as well as dominantly inherited. The correlation between the DFNA2 genotype and phenotype is, however, not that simple [33]. For example, it is difficult to understand that a KCNQ4 mutation, which blocks conductance, would cause a hearing loss that takes years to develop.

So far, mutations in only three genes, KCNA1, KCNQ2, KCNQ3, have been associated with two kinds of nervous system diseases: episodic ataxia (EA) and epilepsy, respectively [34–36]. EA is an autosomal dominant human disorder that produces persistent myokomia and attacks of generalized ataxia. Familial EA has been linked to mutations in the KCNA1 gene. The mutations apparently lead to a reduction (not a loss) in the KCNA1 (Kv1.1) channel function [37]. In comparison, deleting Kv1.1 from mice confers a marked temperature sensitivity to neuromuscular transmission and produces hyperexcitable presynaptic membranes under conditions of stress. This is interesting, because the clinical symptoms of EA may be brought on by physical or emotional stress. Mutations in the KCNQ2 or KCNQ3 genes, on the other hand, have been associated with a benign form of juvenile epilepsy (BFNC) [35,36,38]. KCNQ2 and KCNQ3 may form heteromultimeric channels and probably represent the molecular correlate of M-channels [22]. The mutations most likely lead

to a decrease in M-channel activity. The known role of M currents in the nervous system excitability may reconcile that mutations in KCNQ2/KCNQ3 produce an epileptic disorder. Yet again, many unanswered questions remain in the correlating genotype and BFNC phenotype. In particular, it is not clear why this form of inherited dominant epilepsy disappears within the first year of life.

In summary, phenotypes of Kv channel mutants have been characterized in *C. elegans*, *Drosophila*, mice and humans. The mutations in Kv channel genes have been linked to defects in sensory perception (sound, odor), to abnormal episodic changes in nervous excitability (ataxia, epilepsy, plasticity) and to dysfunction in muscle activity (egg laying, cardiac arrhythmia). Considering the many open slots in Table 1, it is quite possible that soon, more inherited disorders in nervous excitability will be linked to Kv channel mutants. Examples may be deficits in other sensory perceptions than hearing as well as in the occurrence of other stress-related nervous system disorders like migraine, psychosis and schizophrenia. The prospects for the discovery of more Kv channel-related diseases are exciting.

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