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Topical Review

Physiology of EAG K^+ Channels

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Introduction

K^+ channels form a large and diverse group of distinct ion channel families involved in a broad range of physiological functions (Pongs, 1992; Chandy & Gutman, 1995). This review concentrates on the description of the physiological role of members of the EAG family of voltage-gated K^+ channels (in the following, EAG means belonging to the EAG K^+ channel family). The *eag* (*ether-á-go-go*) locus of *Drosophila melanogaster* was the first identified *EAG* gene cloned by chromosomal analysis from a mutant exhibiting leg-shaking behavior during ether anesthesia (Warmke et al., 1991). Using homology screening, related DNA sequences from different species were obtained which could be divided into three different subfamilies: *eag*, *eag*-related gene (*erg*) and *eag*-like K^+ channel (*elk*) (Warmke & Ganetzky, 1994; Ganetzky et al., 1999). The first cloned mammalian *EAG* channels were the mouse *eag1* and the human *erg1* (*HERG*) channel (Warmke & Ganetzky, 1994). Since then, all subfamily members cloned so far have been identified in rat: two *eag* (*eag1*: Ludwig et al., 1994; *eag2*: Saganich et al., 1999), three *erg* (*erg1*: Bauer et al., 1998; *erg2*, *erg3*: Shi et al., 1997) and three *elk* channels (Engeland et al., 1998; Shi et al., 1998) (Fig. 1). Sequence alignments of *Drosophila*, rat, mouse and human EAG channels with sequence databases have shown that they are structurally related to voltage-gated K^+ channels (K_v) and cyclic nucleotide-gated cation channels (Warmke & Ganetzky, 1994). As other K^+ channels, EAG channels are suggested to comprise tetramers formed by the assembly of four subunits, each consisting of six putative transmembrane domains with the S4 domain serving as the main voltage sensor (Fig. 1*A*). EAG channels contain a Per-Arnt-Sim (PAS) domain in the N-terminus (Morais Cabral et al., 1998), a characteristic signature sequence (GFGN) in the P region, and a cyclic nucleotide binding domain (cNBD) within the C-terminus (Fig. 1*A*).

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Identification of Endogenous EAG Channels

It is only since a few years that in an increasing number of cell types native EAG-like currents have been recorded. However, it should be kept in mind that it is impossible to know the exact α- and β-subunit composition of the K^+ channels underlying the recorded endogenous currents. In general, the presence of an endogenous EAG current in a given preparation has been assumed if its biophysical properties are similar to those of a heterologously expressed EAG current and if the respective mRNA transcripts or even channel proteins are present. A more direct proof of endogenous EAG currents can be obtained by using antisense oligonucleotides (Pardo et al., 1999) or dominant-negative mutants (Sanguinetti et al., 1996; Wimmers et al., 2001). The existence of selective erg channel blockers has proved to be a special advantage for the identification and analysis of native erg currents (*see* Schwarz & Bauer, 1999). In the following, characteristic properties of currents mediated by heterologously expressed EAG channels are briefly summarized as a prerequisite for the detection and description of endogenous EAG currents.

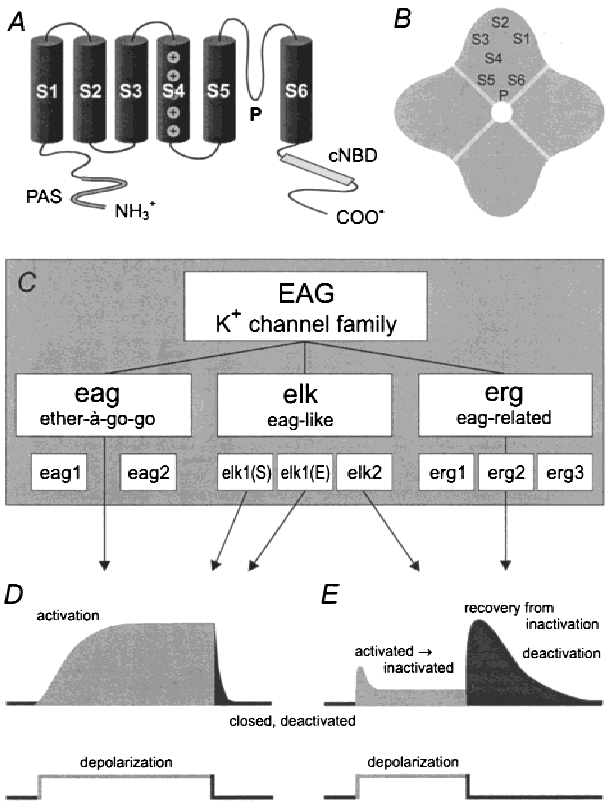

Fig. 1. The *ether-à-go-go* gene K^+ channel family (*EAG*). (*A*) EAG K^+ channel α-subunits consist of six membrane-spanning domains (S1–S6). A Per-Arnt-Sim (PAS) domain is located at the N-terminus and a cyclic nucleotide-binding domain (cNBD) in the C-terminus. (*B*) Proposed tetrameric structure of a K^+ channel. The pore region P and S6 may form the inner core of the channel, S1–S5 the outer parts of the channel with S4 as the voltage sensor. (*C*) The *EAG* K^+ channel family consists of three subfamilies: *eag* (*ether-à-go-go* gene), *elk* (*eag*-like gene) and *erg* (*eag*-related gene). In the rat, each of the subfamilies has 2 or 3 members. (*D*) Schematic drawing of an eag-mediated current. Upon a depolarization a slowly activating noninactivating outward current is elicited. Upon repolarization a small tail current occurs. (*E*) Schematic drawing of an erg-mediated K^+ current elicited by a depolarization. At a negative holding potential, erg K^+ channels are closed and deactivated. A strong depolarization elicits a small current transient followed by a small steady-state outward current because inactivation is faster than activation. Upon repolarization a large transient outward current occurs. Currents mediated by elk1(S) and elk1(E) resemble eag currents, elk2-mediated currents resemble erg currents. The denotation of the three elk subfamily members is explained in the text.

Properties of eag Currents

eag1

The discovery of endogenous putative eag currents was only possible with the knowledge of the distinct biophysical properties of the currents mediated by the heterologously expressed eag channels. Mammalian eag1 channels (rat: Ludwig et al., 1994; mouse: Robertson et al., 1996; human: Occhiodoro et al., 1998; bovine: Frings et al., 1998) and the nematode eag-like egl-2 channel (Weinshenker et al., 1999) activate slowly and do not inactivate during a sustained depolarization (Fig. 1*D*). In contrast, *Drosophila* eag currents exhibit partial inactivation (Robertson et al., 1996). This fact seems to comprise the major difference between *Drosophila* and mammalian eag1 currents since previously described special properties of the *Drosophila* eag channel like Ca^{2+} permeation and gating by cyclic nucleotides (Brüggemann et al., 1993) have not been confirmed (Robertson et al., 1996). The most notable characteristic of eag currents is that the time course of eag current activation is slowed down by negative prepulses (Ludwig et al., 1994; Robertson et al., 1996) and by an increase in the extracellular Mg^{2+} or H^+ concentration (Terlau et al., 1996). This Cole-Moore shift of eag currents is so distinctive that its occurrence is a strong indication for the presence of native eag channels (Fig. 2*A*; Meyer & Heinemann, 1998). Low concentrations of Ni^{2+} have the same effect as Mg^{2+} on heterologously expressed eag1 (Terlau et al., 1996) and native eag1-like channels (Meyer & Heinemann, 1998). Currents mediated by heterologously expressed eag1 channels are effectively blocked by a rise in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) with an $IC_{50} = 67$ nM (Stansfeld et al., 1996; Fig. 2*B*). An increase in $[Ca^{2+}]_i$ also blocks native eag1-like currents in neuroblastoma cells at concentrations significantly lower than 1 μM (Meyer & Heinemann, 1998). The Ca^{2+}-induced eag current reduction has recently been shown to be mediated by binding of calmodulin to a C-terminal domain (Schönherr et al., 2000). An efficient, but unspecific pharmacological block of eag1 currents is obtained by Ba^{2+} and by quinidine (Ludwig et al., 1994), but at present, there is no substance which selectively blocks eag channels and could be used to isolate native eag currents from other K^+ currents.

eag1 Isoforms

From bovine retina two splice variants of the *eag1* channel have been cloned (*bEAG1*, *bEAG2*; Frings et al., 1998). bEAG2 differs from bEAG1 by the insertion of 27 amino acids between S3 and S4. The time course of bEAG2 activation is slower than that of bEAG1, and bEAG1 is less sensitive to Mg^{2+} than bEAG2 (Frings et al., 1998).

eag2

Recently, a second member of the *eag* channel subfamily (*eag2*) has been cloned from rat brain where it seems to be exclusively expressed (Saganich et al., 1999). Like eag1 currents, eag2 currents exhibit a pronounced Cole-

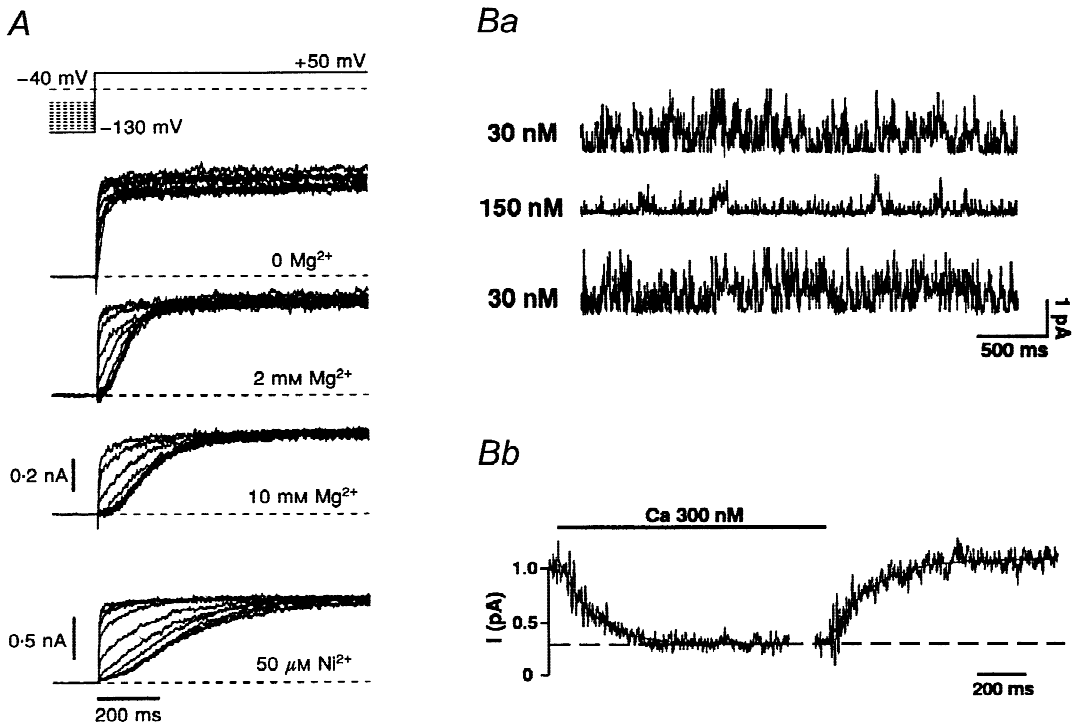

Fig. 2. Properties of eag currents. (*A*) Activation kinetics depend on the holding potential and the extracellular Mg^{2+} concentration. Endogenous eag1-like membrane currents were elicited in a human neuroblastoma cell in response to depolarizations to 50 mV from holding potentials which varied from −130 to −40 mV in steps of 10 mV in external solutions containing the indicated concentrations of Mg^{2+} or 50 μM Ni^{2+}. The trace with the slowest activation corresponds to −130 mV, that with the fastest activation to −40 mV prepulse potential. Reproduced with permission from Meyer & Heinemann (1998). (*Ba*) Ca^{2+}-induced block of rat eag1 channels heterologously expressed in CHO cells. Steady-state channel activity measured in inside-out patches at 0 mV in the presence of 30 nM free $[Ca^{2+}]$, after changing to a solution with 150 nM free $[Ca^{2+}]$ and on return to 30 nM free $[Ca^{2+}]$. (*Bb*) Ensemble rat eag1 currents from a patch containing at least four channels, showing the response to a step increase of $[Ca^{2+}]$ in the bath from 30 to 300 nM and back. Current traces were fitted with monoexponential functions with time constants of 131 and 175 msec, respectively. Reproduced with permission from Stansfeld et al. (1996).

Moore shift and they are blocked by low concentrations of cytosolic Ca^{2+} (Saganich et al., 1999; Ludwig et al., 2000). However, the activation threshold of eag2 channels is much more negative (−100 mV) than that of rat eag1 channels (−50 mV; Ludwig et al., 1994), and eag2 channels exhibit only a weak potential dependence.

β-Subunits Coupling to eag1

So far, a few β-subunits have been found to interact with eag1 channels and to affect their biophysical properties. The *Drosophila* β-subunit hyperkinetic increases the current amplitude mediated by *Drosophila* eag1 channels, slightly accelerates current activation and slows inactivation (Wilson et al., 1998). Hyperkinetic also moderately increased mouse eag1 currents and accelerated current activation (Wilson et al., 1998). The protein epsin was isolated from rat brain and has been found to bind to eag1 channels, thereby decreasing the probability of channel opening at potentials near the resting potential (Piros, Shen & Huang, 1999). In contrast, binding of the protein KCR1 to eag channels leads to an increase in the eag current amplitude by induction of a faster eag channel activation and a shift of the activation curve by 10 mV to more negative membrane potentials (Hoshi et al., 1998).

Properties of erg Currents

erg1

Heterologously expressed HERG and erg1 channels from other species mediate membrane currents exhibiting characteristic kinetic properties. Upon depolarizations to potentials below 0 mV the time course of erg current activation is slow reaching a steady state only after several seconds (Snyders & Chaudhary, 1996; Wang et al., 1997). Stronger depolarizations elicit only small outward currents, whereas large transient currents occur upon repolarization (Fig. 1*E*). This phenomenology of erg currents has been explained by inverse gating

kinetics compared to classical *Shaker*-like K_v channels, i.e., inactivation is faster than activation and recovery from inactivation is considerably faster than deactivation (Trudeau et al., 1995; Smith, Baukrowitz & Yellen, 1996; Spector et al., 1996*b*; Wang et al., 1997). In this context, it should be mentioned that I_{Kr}, the rapidly activating delayed rectifying K^+ current of the heart, was the first native EAG current of which essential biophysical properties were described (Shibasaki, 1987; Sanguinetti & Jurkiewicz, 1990) well before HERG, the channel mediating I_{Kr}, was cloned (Warmke & Ganetzky, 1994). The fast erg channel inactivation which is due to a C-type inactivation mechanism (Schönherr & Heinemann, 1996; Smith et al., 1996; Herzberg, Trudeau & Robertson, 1998; Fan et al., 1999) transforms erg channels into channels with inward rectification. Since the depolarization-induced "apparent" erg current activation always reflects activation as well as inactivation, the "true" time course as well as voltage dependence of activation could only be determined with tail current protocols (Shibasaki, 1987; Sanguinetti & Jurkiewicz, 1990; Wang et al., 1997). Due to the slow activation and deactivation with time constants up to 15 sec, very long conditioning pulses have to be used to measure real steady-state activation (Wang et al., 1997; Bauer et al., 1998; Schönherr et al., 1999).

erg1 channels are well characterized by their pharmacological profile. Most importantly, they can selectively be blocked by methanesulfonanilides like E-4031, WAY-123,398 and dofetilide (Sanguinetti et al., 1995; Spector et al., 1996*a*; Snyders & Chaudhary, 1996). A scorpion toxin (ergotoxin) has recently been described to selectively and reversibly block erg channels (Gurrola et al., 1999). Beside the strong expression of *erg1* in the heart, *erg1* is widely expressed in neuronal as well as nonneuronal tissue (Wymore et al., 1997; Bauer et al., 1998).

erg1 Isoforms

In addition to Merg1a, the mouse homologue of HERG, two splice variants were cloned from mouse (Lees-Miller et al., 1997; London et al., 1997). One isoform (Merg1a′) lacks the first 59 of 376 amino acids of the cytoplasmic N-terminus of Merg1a (London et al., 1997). The other isoform (Merg1b) as well as its human homologue has a very short (36 amino acids) and unique N-terminus and its mRNA expression is restricted to the heart (Lees-Miller et al., 1997; London et al., 1997). Merg1a′ and Merg1b deactivate with a faster time course than Merg1a and it has been suggested that erg1b contributes to I_{Kr} (Lees-Miller et al., 1997), possibly by the formation of heteromultimeric channels with erg1 (London et al., 1997). The expression level of erg1b could therefore determine the deactivation kinetics of I_{Kr} and, as a consequence, the duration of the ventricular action potential (London et al., 1997). However, erg1b has not been detected in heart tissue at the protein level (Pond et al., 2000). The accelerated deactivation time course of erg1a′ and erg1b is readily explained by the truncated or even absent PAS or EAG domain which is formed by the first 135 amino acids of the HERG N-terminus and has been considered a defining feature of EAG K^+ channels (Morais Cabral et al., 1998; Viloria et al., 2000). This domain and especially its most distant part have been found to be critical for the slow deactivation of HERG channels, presumably by binding to the S4–S5 linker (Schönherr & Heinemann, 1996; Morais Cabral et al., 1998; Wang et al., 1998; Chen et al., 1999; Viloria et al., 2000; Wang, Myers & Robertson, 2000).

In addition to the N-terminal splice variants of erg1, a C-terminal splice variant has been identified in human heart (*$HERG_{USO}$*; Kupershmidt et al., 1998) which is identical to *HERG* up to a splice site within the cNBD, followed by a novel sequence. Although the heterologous expression of $HERG_{USO}$ alone did not yield functional channels, the coexpression of $HERG_{USO}$ with HERG1 led to a decrease in the amplitude as well as to changes in the kinetics and voltage dependence of activation of the resulting currents.

erg Subfamily Members

In addition to rat *erg1* (Bauer et al., 1998), two other *erg* channel cDNAs expressed in the nervous system have been cloned from rat (*erg2*, *erg3*; Shi et al., 1997). The kinetics of erg2 currents roughly resemble those of erg1 currents. Clearly different are erg3 currents which exhibit less pronounced inward rectification due to considerably faster activation and deactivation kinetics and slower inactivation kinetics (Shi et al., 1997). The midpoint for isochronal channel activation determined with prepulses of the same duration (5 sec) is shifted by about 20 mV among the channels, from −44 mV (erg3) to −20 mV (erg1) and to −3.5 mV (erg2; Shi et al., 1997). The subunits of the three different rat erg channels have recently been found to form heteromultimeric channels, but they did not form heteromultimers with members of the two other EAG subfamilies (eag1 and elk1; Wimmers et al., 2001). Since all three erg channels are blocked by E-4031 with a similar high sensitivity (Shi et al., 1997), this criterium could be used for the identification of native erg currents.

β-Subunits Associated with erg1

Using heterologous expression systems HERG1 has been found to coimmunoprecipitate with the β-subunits MinK and MiRP1 (McDonald et al., 1997; Abbott et al., 1999). Binding of MinK to HERG increases current amplitude

(Yang, Kupershmidt & Roden, 1995) probably due to an increase in the fraction of active HERG channels incorporated into the plasma membrane (McDonald et al., 1997). In addition, MinK shifts the HERG activation curve to more negative potentials and increases steady-state inactivation (McDonald et al., 1997; Bianchi et al., 1999). After coexpression of MiRP1 with HERG, membrane currents were recorded resembling more closely I_{Kr} than the currents after expression of HERG alone. MiRP1 slightly shifted the HERG activation curve to more positive potentials, accelerated deactivation and decreased single channel conductance (Abbott et al., 1999). The binding of MinK or MiRP1 to HERG has also been shown to influence the modulation of HERG channels by cAMP binding and PKA phosphorylation (Cui et al., 2000). Recently, coexpression of the β-subunit MiRP2 (KCNE3) with HERG in *Xenopus* oocytes has been reported to drastically suppress HERG currents (Schroeder et al., 2000). The *Drosophila* β-subunit hyperkinetic also affects HERG currents, though these effects were apparent only several days after *Xenopus* oocyte injection. The effects include a huge increase in current amplitude, a slight acceleration of activation kinetics, a slowing of deactivation as well as a small shift of the activation curve to more positive potentials (Wilson et al., 1998).

Properties of elk Currents

Although the first *elk* channel was cloned from *Drosophila* already in 1994 (Warmke & Ganetzky), no data are available about its functional expression. More recently, three different *elk* channels have been cloned from a rat cortex cDNA library and their membrane currents characterized after heterologous expression (Engeland et al., 1998; Shi et al., 1998). Unfortunately, different sequences were denoted as *elk*1 in these reports. The sequence of *elk*1 reported by Shi et al. (1998; denoted here as *elk*1 (S)) is identical with that of the *elk*3 fragment of Engeland et al. (1998), whereas *elk*1 by Engeland et al. (denoted here as *elk*1 (E)) is another distinct member of the elk subfamily. The full length *elk*2 reported by Engeland et al. (1998) corresponds to the partial *elk*2 sequence of Shi et al. (1998). A corresponding cDNA has also been cloned from mouse (*Melk*2; Trudeau et al., 1999). In the brain, mRNAs for all three elk subunits have been detected. During brain maturation, the expression level of *elk*1 (E) is relatively constant, whereas the expression of *elk*2 appears to be upregulated and that of *elk*1 (S) downregulated (Engeland et al., 1998). elk1(S) as well as elk1 (E) mediate slowly activating K^+ currents similar to eag currents. However, elk currents do not exhibit the characteristic Cole-Moore shift of eag channels (Engeland et al., 1998; Shi et al., 1998; Trudeau et al., 1999). Currents mediated by elk1 (S) are activated positive to −40 mV, whereas elk1 (E) currents activate already at very negative membrane potentials (positive to about −90 mV). The macroscopic elk2 currents resemble erg currents (Engeland et al., 1998), and their fast inactivation has also been shown to result from C-type inactivation (Trudeau et al., 1999). However, compared to erg channels, the voltage dependence of elk2 current activation is shifted to more positive potentials (Engeland et al., 1998). A characteristic difference from erg channels is that all elk channels are insensitive to E-4031 (Engeland et al., 1998; Shi et al., 1998; Trudeau et al., 1999).

Physiological Roles of the EAG K^+ Channel Family

The molecular analysis of behavioral mutants in *Drosophila melanogaster* led to the detection of the *eag* locus initiating the search for and detection of the different members of the *EAG* K^+ channel family in invertebrates and vertebrates. The genome sequencing project in *Caenorhabditis elegans* yielded the identification of eight different families of K^+ channels in this animal (Wei, Jegla & Salkoff, 1996) which also allowed studies of behavioral mutants induced by defined K^+ channel mutations (Elkes et al., 1997; Johnstone et al., 1997). Below we describe examples of abnormal behavioral phenotypes in flies and nematodes induced by mutations in the *EAG* family of K^+ channel genes.

Phenotypes of *Drosophila* eag and erg Mutants

Mutants of the *eag* locus of *Drosophila melanogaster* exhibit rhythmic leg-shaking during ether anesthesia (Ganetzky & Wu, 1983). In larvae of these mutants a high frequency of spontaneously firing action potentials in motor nerve fibers and an increase in the amplitude and duration of end plate potentials were found, indicating an enhanced transmitter release at the neuromuscular junction as compared with normal larvae (Wu et al., 1983; Ganetzky & Wu, 1983). These findings were the first indication that the *eag* locus encodes a K^+ channel and that a dysfunction in a member of the EAG K^+ channel family induces an increase in neuronal excitability. In muscles of *eag* mutant larvae a reduction in the amplitude of two voltage-dependent and two Ca^{2+}-activated K^+ currents was found (Zhong & Wu, 1991). These changes suggested that the eag subunit may act as a modulator of K^+ channels (Zhong & Wu, 1993). Coexpression experiments in *Xenopus* oocytes indicated that indeed an interaction between eag subunits and *Shaker* channels may take place under certain conditions (Chen et al., 2000).

The eag-mediated K^+ conductance seems also to be involved in odor transduction. In *eag* mutants the pro-

portion of antennal neurons sensitive to a subset of odorants was reduced and fewer odorant-induced inhibitory responses as well as defects in the cyclic-nucleotide- and Ca^{2+}-dependent neuronal processes involved in odor transduction occurred (Dubin, Liles & Harris, 1998).

In addition to the *eag* locus (Drysdale et al., 1991) and the *elk* gene (Warmke & Ganetzky, 1994) a member of the *eag*-related K^+ channel gene (*erg*), the third subfamily of the *EAG* K^+ channel family, has been identified as the seizure locus (*sei*) in *Drosophila* (Titus et al., 1997). Mutations of *sei* are characterized by a temperature-sensitive paralysis combined with hyperactivity in the flight motor pathway.

Behavioral Phenotypes of a *Caenorhabditis Elegans* eag-like (egl-2) Mutant

In *Caenorhabditis elegans* a mutation of the eag channel protein encoded by the *egl*-2 gene induces behavioral defects characterized by inhibition of the egg-laying and enteric muscle contraction as well as by a defect in the chemotaxis behavior to volatile odorants (Weinshenker et al., 1999). All of these mutant phenotypes were rescued after treatment with the tricyclic antidepressant imipramine. Weinshenker et al. (1999) cloned and functionally expressed the WT and mutated *egl*-2 gene and found that the mutation of this eag-like channel induced a shift of the activation curve by 40 mV to more negative membrane potentials as compared to that of WT egl-2 channels, thereby inducing an inappropriate channel opening (gain-of-function mutation). Rescue of the mutant behavior after treatment is likely due to a blockage of the mutated egl-2 channels by imipramine.

The above examples show that EAG K^+ channels fulfill important functions in the modulation of cellular excitability properties underlying different behavioral phenotypes. The next step is the functional analysis of membrane currents mediated by the various members of the EAG K^+ channel family at the cellular level. In the following, examples of the physiological roles of putative eag and erg currents in different mammalian tissues will be described.

Physiology of eag K^+ Currents

Endogenous eag currents have been reported in myoblasts and various tumor cells. Although eag subunits are specifically expressed in the adult rat brain, there are no reports about eag-mediated currents in normal neuronal tissue and the physiological role of eag in the central nervous system has still to be elucidated. However, there are indications that eag currents may be present in the retina as described below, and recently, *eag1* mRNA has been found to be expressed in certain cells of the cochlea (Lecain et al., 1999).

An eag-like Current Takes Part in the Dark-Current Loop of Photoreceptors

In rod photoreceptors, the dark-current is mediated by cGMP-gated cation channels in the outer segments of the receptors. The current loop is closed by an outward current through K^+ channels in the inner segment mediating a K^+ current which has been studied in salamander rod cells and called I_{Kx} (Beech & Barnes, 1989). Like eag currents, I_{Kx} is a noninactivating K^+-selective current which is activated at potentials > −50 mV. Both *eag*1 isoforms (*bEAG*1 and *bEAG*2) are expressed in bovine photoreceptors and retinal ganglion cells as shown by *in situ* hybridization (Frings et al., 1998). The similarities between I_{Kx} and heterologously expressed bEAG1 and bEAG2 currents suggest that eag subunits take part in forming the channels mediating I_{Kx}. However, there are also differences between both currents, e.g., deactivation of I_{Kx} is much slower than deactivation of the bEAG currents. These differences could be explained by the binding of auxiliary subunits to the native eag channels, thereby changing their gating properties.

Expression of eag Channels in Relation to Myoblast Differentiation

Induction of differentiation of human myoblasts is accompanied by hyperpolarizing changes of their resting potential through the sequential expression of two different types of K^+ channels. From values of approximately −10 mV measured in undifferentiated proliferating myoblasts the resting potential is shifted to about −30 mV when the cells start to differentiate. This hyperpolarization is correlated with an increase in the expression of h-eag1 channels presumably mediating the noninactivating K^+ current ($I_{K(NI)}$). Subsequently, slightly before myoblast fusion, the expression of eag1 channels decreases and that of a classical inward-rectifying K^+ channel increases driving the resting potential to values between −55 and −70 mV in multinucleated myotubes (Bijlenga et al., 1998; Occhiodoro et al., 1998; Liu et al., 1998). This transient expression of eag1 channels explains the lack of expression of eag1 in adult human skeletal muscle (Occhiodoro et al., 1998) and indicates that eag1 expression is a cell cycle-related phenomenon since myoblast fusion is intimately coupled with irreversible cell-cycle arrest.

The eag Current in Tumor Cells and its Role in Malignant Transformation

In human SH-SY5Y neuroblastoma cells (Meyer & Heinemann, 1998) and in distinct melanoma cell lines (Meyer et al., 1999) eag currents have been described exhibiting the characteristic biophysical properties of rat eag1 currents (Ludwig et al., 1994). As in myoblasts the

expression of the h-eag channels in neuroblastoma cells is related to the cell cycle, because after synchronization of the cells with retinoic acid in the G1 phase the eag current amplitude decreased to less than 5% of the control, whereas the amplitude of the delayed rectifying K^+ current increased (Meyer & Heinemann, 1998). The efficient eag current block by an increase in $[Ca^{2+}]_i$ in melanoma cells (Meyer et al., 1999) as well as upon application of acetylcholine in neuroblastoma cells (Meyer & Heinemann, 1998) could be important for various intracellular signal cascades which mediate an increase in $[Ca^{2+}]_i$, either by release of Ca^{2+} from intracellular stores or by an influx of Ca^{2+} through voltage-gated Ca^{2+} channels.

It was also found that eag is expressed ectopically in several human cancer cell lines and that inhibition of eag expression causes a significant reduction of cell proliferation (Pardo et al., 1999). These data together with the cell cycle-dependent expression of eag channels, suggest a direct involvement of eag channels in cell proliferation and prompt the possibility that eag channels participate in the transformation of normal cells into tumor cells. This idea was supported by the result that transfection of CHO cells with eag channels led to an increased proliferation rate (Pardo et al., 1999). Since eag channels are expressed normally only in the brain, these results may have important clinical implications for the detection of tumors outside the brain. Another example for the relation of eag channels to the cell cycle was derived from studies of heterologously expressed eag channels. Dependent on the phases of the cell cycle, eag channels change their permeability properties, being either permeable to Cs^+ or exhibiting rectification due to a block by intracellular Na^+ (Brüggemann et al., 1997; Pardo et al., 1998). The cell cycle-related changes of eag channels are presumably due to a reorganization of the cytoskeleton during the G2/M transition (Camacho et al., 2000).

These examples of native eag-like currents show that they are involved in the setting of the resting potential. However, the causal relationship between the resting potential and cell cycle-dependent cellular processes like proliferation and differentiation is not clear. Another possible function of endogenous eag currents could be due to the Cole-Moore-shift. In excitable cells the dependence of the time course of eag current activation on extracellular Mg^{2+} and the resting potential could provide a possibility to modulate the time course of action potential repolarization.

Physiology of erg K^+ Currents

Function of the erg Current in the Heart

The delayed rectifying K^+ current of ventricular myocytes consists of two components, the rapidly (I_{Kr}) and the slowly (I_{Ks}) activating K^+ current (Sanguinetti & Jurkiewicz, 1990). I_{Kr} is suggested to be mediated by erg1 channels (Sanguinetti et al., 1995) to which β-subunits like MiRP1 (Abbott et al., 1999) may be attached (*see above*). The erg1 channel mRNA is expressed almost equally abundantly in the sinoatrial node, atrium and ventricle of rabbit heart (Wymore et al., 1997). At the protein level, the relative amount of erg1 expression in atrium and ventricle is different in rat and human heart (Pond et al., 2000). The properties of I_{Kr} have been studied in sinoatrial node cells (Shibasaki, 1987; Ito & Ono, 1995; Ho et al., 1996; Zaza et al., 1997) as well as in atrial (Liu et al., 1996) and ventricular myocytes (Sanguinetti & Jurkiewicz, 1990; Clay et al., 1995; Heath & Terrar, 1996). In the sinoatrial node, the erg1 current with its slow time course of deactivation seems to contribute to the ionic mechanisms underlying pacemaking (Verheijck et al., 1995; Zaza et al., 1997). In atrial and ventricular myocytes, I_{Kr} has an important function in plateau formation and repolarization of the action potential. During the plateau phase of the ventricular action potential I_{Kr} has only a small amplitude (*see* Fig. 3*A*). This function of I_{Kr} supports the formation of the plateau potential and is a consequence of its inward-rectifying properties. As repolarization proceeds, a transient increase in the erg outward current occurs due to fast recovery from inactivation and slow deactivation (Fig. 3*A*). This erg current together with the activation of the classical cardiac inward rectifier (I_{K1}) repolarizes the action potential. Studies using the action potential-clamp have shown that erg1 contributes current throughout the return of the action potential to the resting potential (Fig. 3*A*; Hancox, Levi & Witchel, 1998; Zhou, Z. et al., 1998).

In guinea-pig ventricular myocytes the amplitude of I_{Kr} is increased by isoprenaline or forskolin due to a reduction in the steady-state inactivation (Heath & Terrar, 2000). The increase in I_{Kr} could be inhibited by an inhibitor of PKC. The authors therefore assume that a reduction in C-type inactivation due to phosphorylation of the channel protein by PKC is responsible for the increase in I_{Kr}. The complex intracellular pathway activated by binding of isoprenaline to β-adrenoceptors might consist of a cAMP-mediated increase in $[Ca^{2+}]_i$ via an increased influx of Ca^{2+} through voltage-dependent Ca^{2+} channels. The increase in $[Ca^{2+}]_i$ could then activate PKC.

Reduction of I_{Kr} due to a mutation in *HERG* prolongs the cardiac action potential. An extreme action potential lengthening can induce early afterdepolarizations, an increased tendency to heart arrhythmia and the occurrence of "torsade de pointes", eventually leading to ventricular fibrillation and sudden death (Curran et al., 1995). This long QT-syndrome (LQT-2) can be inherited or acquired. The inherited form is caused by a number of mutations in *HERG* leading to reduced I_{Kr} either by loss of function or altered function of the HERG

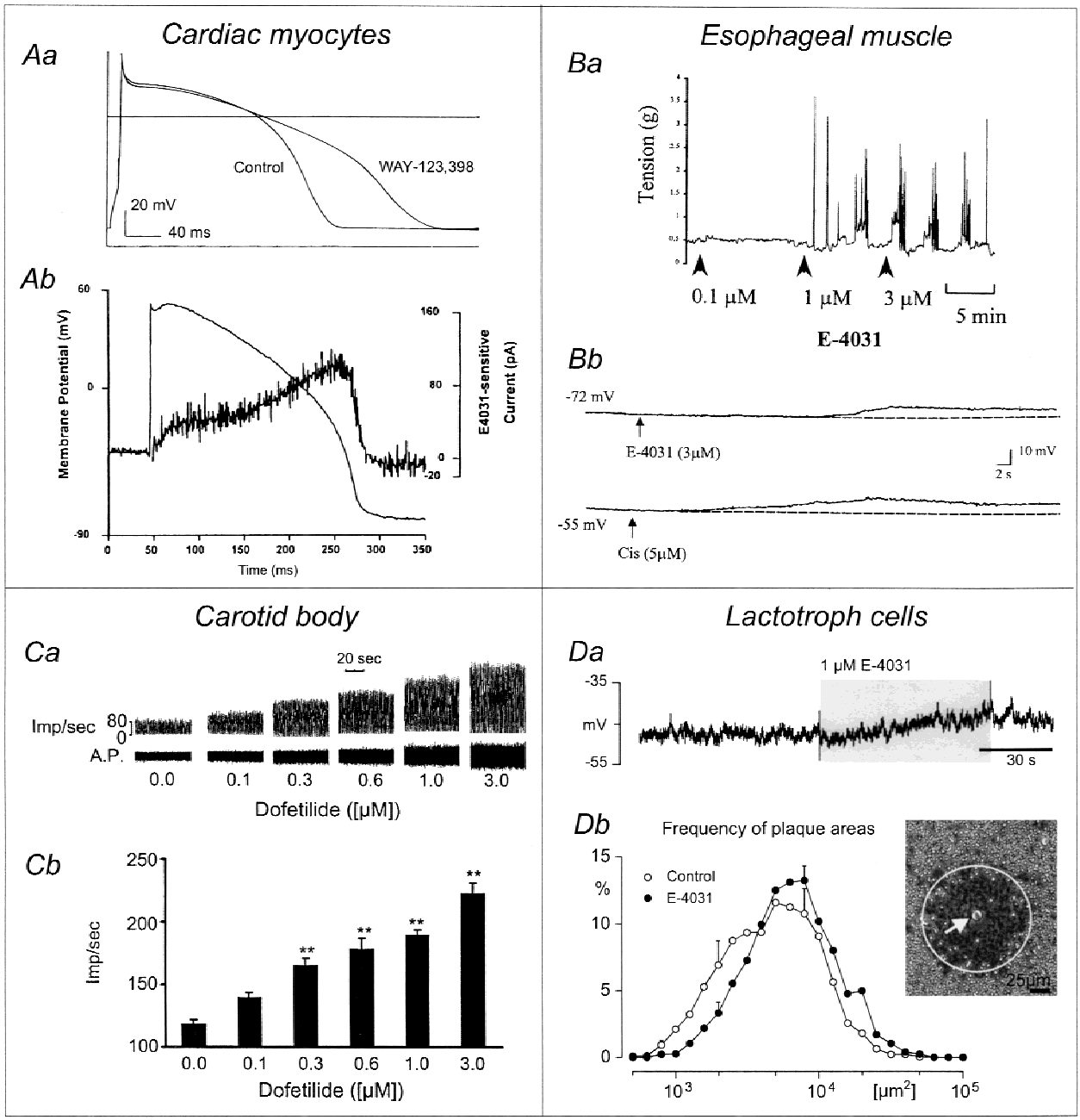

Fig. 3. Examples for different physiological functions of erg currents revealed by the use of specific erg channel blockers. (*Aa*) Recording of an action potential from a cat ventricular myocyte. The class III antiarrhythmic WAY-123,398 (0.3 µM) prolonged the action potential. Modified from Spinelli et al. (1993). (*Ab*) Measurement with an action potential-clamp in an isolated guinea-pig ventricular myocyte. The holding potential was −40 mV to inactivate Na^+ channels, Ca^{2+} channels were blocked by nitrendipine (10 µM) and I_{K1} was attenuated by Ba^{2+} (100 µM). Membrane currents were elicited with a series of five to ten action potentials as command potential before and after application of E-4031. The average E-4031-sensitive current is superimposed on the command action potential waveform. From Hancox et al. (1998). (*Ba*) A block of the erg-like current increases esophageal muscle tension. Recording of developed tension from an isolated esophageal muscle strip. At concentrations higher than 1 µM, E-4031 induced phasic contractions. (*Bb*) Microelectrode recording of the resting potential in two different muscle cells from esophageal muscle strip. Blockers of the erg current (E-4031 and cisapride) induced a depolarization. From Akbarali et al. (1999). (*Ca*) Block of glomus cell erg-like current increases impulse frequency recorded from the carotid sinus nerve innervating the carotid body. In the isolated carotid body dofetilide increased sensory activity in a dose-dependent manner. Imp/sec, rate meter output; A.P., action potential. (*Cb*) Summary of data (means ± SEM; $n = 7$) obtained in experiments as shown in *Ca*. From Overholt et al. (2000). (*D*) Prolactin secretion from single lactotrophs is increased by E-4031. (*Da*) E-4031 induced a depolarization of the resting potential recorded in a native lactotroph. (*Db*) Measurement of the E-4031-induced increase in prolactin secretion from single lactotrophs with the reverse hemolytic plaque assay (RHPA). Incubation of lactotrophs with E-4031 induced a shift in the frequency distribution to larger plaque areas. From Bauer et al. (1999). All data here are reproduced with permission from the respective authors and publishers.

protein (Sanguinetti et al., 1996; Zhou, Z. et al., 1998; Chen et al., 1999). An inherited LQT syndrome can also be caused by a mutation in *MiRP*1 (Abbott et al., 1999). The acquired form of LQT-2 is induced by a pharmacological block of I_{Kr} also resulting in a prolongation of the cardiac action potential (Fig. 3*A*). This prolongation suppresses ventricular tachyarrhythmia, and therefore class III antiarrhythmics are used therapeutically to prolong ventricular refractoriness and prevent ectopic activity arising from reentrant electrical circuits (Sanguinetti & Keating, 1997). However, especially under stress the cardiac action potential is further prolonged due to an increased influx of Ca^{2+}. The prolonged action potential favors the occurrence of afterdepolarizations and the fatal symptoms described above. The acquired LQT-2 syndrome does not only occur during treatment with class III antiarrhythmics, but also upon treatment with other widely used pharmacological substances which have been shown to block I_{Kr}/HERG currents (reviewed by Tamargo, 2000), such as neuroleptics (Suessbrich et al., 1997), histamine receptor antagonists (Suessbrich et al., 1996), Ca^{2+} channel blockers (Chouabe et al., 1998), prokinetic agents (Mohammad et al., 1997), sulfonylurea antidiabetic drugs (Rosati et al., 1998), fungicides (Dumaine, Roy & Brown, 1998), antimalarial agents (Tie et al., 2000) or phosphodiesterase inhibitors (Geelen et al., 2000).

The erg Current Contributes to the Maintenance of the Resting Potential

The resting potential of muscle cells or neurons with values between −60 and −80 mV is mediated by classical inward-rectifying K^+ channels (K_{ir}). These negative potentials are maintained because classical inward rectifiers do not inactivate, therefore their small outward currents shift the membrane potential towards the K^+ equilibrium potential. However, there are also cell types which are devoid of classical inward rectifier channels, but instead possess erg channels. In these cells the erg current contributes to the maintenance of the resting potential which is less negative due to erg channel deactivation at membrane potentials more negative than about −50 mV. The examples described below take advantage of specific erg channel blockers to demonstrate that erg currents contribute to the maintenance of the resting potential. The depolarization of the resting potential by erg channel block is correlated to cellular functions like muscle contraction, O_2 sensing and hormone secretion. In addition, erg currents have been measured in embryonic cells and tumor cells where they also maintain or set the resting potential. In spite of their defined physiological roles, the density of the endogenous erg currents is so small that these currents had to be analyzed in elevated external K^+ solution to increase the current amplitude.

An erg Current in Astrocytes May be Involved in K^+ Homeostasis

The expression of erg1 channels and presence of erg-like currents has recently been reported in hippocampal and spinal astrocytes (Emmi et al., 2000). In this study the immunocytochemical staining indicated that the distribution of the erg channel protein in the hippocampus is confined to astrocytes and may only occur at a very low density in the cell bodies and proximal dendrites of pyramidal neurons and dentate granule cells. The erg channels could be involved in K^+ homeostasis, since in the presence of E-4031 no buffering of an increase in the extracellular K^+ concentration induced by enhanced neuronal firing of action potentials occurred.

Involvement of the erg Current in Esophageal Smooth Muscle Contraction

The presence of an erg1 immunoreactivity and an erg-like current has been demonstrated in opossum esophageal smooth muscle cells (Akbarali et al., 1999). Since this erg current mediates a small steady-state current in the range of the resting potential it is suggested to take part in the maintenance of the resting potential of these cells. Accordingly, a pharmacological block of the erg current depolarized the membrane potential and induced spontaneous contractions (Fig. 3*B*), presumably due to an increase in the $[Ca^{2+}]_i$ due to the opening of voltage-dependent Ca^{2+} channels.

Possible Involvement of the erg Current in O_2 Sensing

In glomus cells of the rabbit carotid body an erg current is believed to contribute to the maintenance of the resting membrane potential which is between −40 and −65 mV in these cells (Overholt et al., 2000). Activation of the erg current in glomus cells is half-maximal at −44 mV and the threshold for current activation is positive to −70 mV. Dofetilide (150 nM) depolarizes the mean resting potential from −48 to −35 mV and induces an increase in $[Ca^{2+}]_i$ as well as in the spike frequency of the afferent nerve fibers, mimicking the effects induced by hypoxia on the spike frequency of the carotid sinus nerve (Overholt et al., 2000; Fig. 3*C*). Based on these data erg channels are candidates for O_2 sensing, because the erg protein contains a PAS domain that is known to be sensitive to O_2 in other proteins (Pellequer, Brudler & Getzhoff, 1999). Alternatively, hypoxia could modulate K^+ currents by affecting the redox state of the cell or by altering the level of reactive oxygen species (ROS). In line with this idea, ROS have been shown to increase HERG currents (Taglialatela et al., 1997). If hypoxia would de-

crease the erg current this could lead to a depolarization resulting in an increase in sensory activity.

Involvement of the erg Current in the Regulation of Prolactin Secretion in Lactotrophs

Like in various other neuroendocrine cells, hormone secretion from lactotrophs of the anterior pituitary is regulated by changes in their excitability (reviewed by Corrette, Bauer & Schwarz, 1995). TRH stimulates prolactin secretion by a membrane depolarization which may be accompanied by an increase in the rate of Ca^{2+} action potential firing leading to an increase in $[Ca^{2+}]_i$ (Corrette et al., 1995). In two subclones of rat somatomammotroph GH cells (GH_3/B_6: Bauer, Meyerhof & Schwarz, 1990; GH_3: Barros et al., 1992) as well as in native lactotrophs from rat primary culture (Corrette, Bauer & Schwarz, 1996; Schäfer et al., 1999) an inwardly rectifying K^+ current has been described which contributes to the maintenance of the resting potential (Fig. 3*D*a) and is blocked by TRH. This K^+ current is carried by erg channels (Bauer et al., 1998; Wimmers et al., 2001). The candidate subunits for the formation of erg channels in GH_3/B_6 cells are erg1 and erg2, and in native lactotrophs erg1, erg2 and erg3 (Schäfer et al., 1999). These subunits are able to form heteromultimeric erg channels (Wimmers et al., 2001). The TRH-induced reduction of the erg current is mediated by a G protein-coupled intracellular signal cascade involving an as yet unknown intracellular messenger. The erg current reduction is mainly due to a shift in the erg current activation curve to more positive membrane potentials and a decrease in the maximal amplitude of the erg current (Bauer et al., 1990; Schledermann et al., 2001). Although it is very likely that a phosphorylation is involved in the TRH-induced signal cascade (Barros et al., 1993), activation of the protein kinases C and A do not mediate this effect (Bauer et al., 1994; Schäfer et al., 1999; Schledermann et al., 2001). This is not in agreement with the results obtained by studying the modulation of heterologously expressed HERG channels (Barros et al., 1998; Thomas et al., 1999) and demonstrates that the results obtained in a heterologous expression system cannot always be transferred to the native cells.

The increase in prolactin secretion induced by the erg current block in lactotrophs has been measured with the reverse hemolytic plaque assay (RHPA; Fig. 3*D*; Bauer et al., 1999). The plaque area is a semiquantitative measure of prolactin secretion from a single lactotroph. E-4031 enhances prolactin secretion due to an increase in the number of plaque-forming lactotrophs as well as to an increase in the amount of hormone secreted from the individual lactotrophs, as indicated by the shift of the frequency distribution to larger plaque areas (Fig. 3*D*). Since TRH effectively reduces the erg current, these data also demonstrate the functional importance of the erg current in the TRH-induced increase in prolactin secretion.

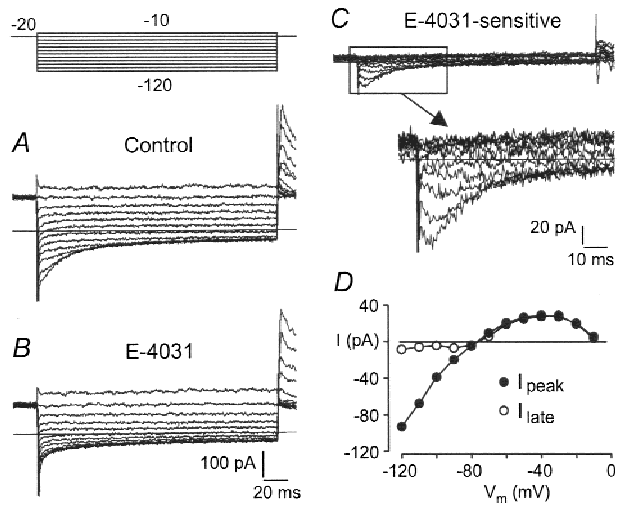

Fig. 4. The endogenous erg-like current of a rat lactotroph cell isolated as the E-4031-sensitive current. Membrane currents recorded from a lactotroph in primary culture in external 5 mM K^+ solution using the pulse protocol shown in the upper panel. Membrane currents recorded under control conditions (*A*) and after application of 10 μM E-4031 (*B*). (*C*) The E-4031-sensitive current was isolated by subtraction of the currents measured in the presence of the drug (*B*) from the control currents (*A*). (*D*) Voltage dependence of the peak (I_{peak}) and the late (I_{late}, measured at the end of the 200 msec test pulses) amplitudes of the E-4031-sensitive current. Reproduced with permission from Bauer et al. (1999).

The properties of the inward-rectifying K^+ current ($I_{K,IR}$) in GH_3/B_6 cells have been described before this current was identified as an erg current (Bauer et al., 1990). $I_{K,IR}$ has only later been isolated as the E-4031-sensitive current from the other K^+ currents in GH_3/B_6 cells (Weinsberg et al., 1997) and in native lactotrophs from primary culture (Bauer et al., 1999; Schäfer et al., 1999). The E-4031-sensitive current of a native rat lactotroph measured in 5 mM external K^+ solution is shown in Fig. 4. The fully-activated current-potential relationship exhibits a maximum outward current amplitude near −40 mV which correlates with the value of the resting potential in lactotrophs (Bauer, 1998; Bauer et al., 1999). As is typical for an inward-rectifying K^+ current, at more positive potentials the outward K^+ current decreases (Fig. 4). Figure 4 also demonstrates the difficulty to detect native erg currents in low external K^+ solutions and the necessity of the use of specific erg channel blockers.

erg Currents in Embryonic Neuronal Crest Cells

In embryonic neuronal cells originating from quail neural crest cells erg channels were found to be expressed only during the immature stages of neural differentiation,

whereas at later stages erg channels vanish and classical inward-rectifying K^+ channels appear (Arcangeli et al., 1997). The sequential expression of the two types of K^+ channels is reflected by two different levels of the resting potential, a low resting potential of about −35 mV during the immature stage and values of about −55 mV after differentiation (Arcangeli et al., 1997). The substitution of an erg current by a classical inward-rectifying K^+ current was also observed in embryonic neural crest cells with time in cell culture. These data indicate that erg channel expression may be restricted to an immature and transient stage of neuronal differentiation.

In Neuroblastoma Cells the erg Current Can Be Related to Different Functions

Endogenous erg currents have been studied in neuroblastoma cells of both human and murine origin. It was found that there is a relationship of the properties of erg channels to cellular processes like the cell cycle (Arcangeli et al., 1995; Faravelli et al., 1996; Meyer & Heinemann, 1998) and neuritogenesis (Arcangeli et al., 1993, 1996). Neuroblastoma cells exhibit a large variability in the voltage dependence of erg current activation and in the resting potential (Arcangeli et al., 1995). After cell cycle synchronization the variability in both parameters was reduced, indicating that erg channels in neuroblastoma cells determine the resting potential and that the erg channel properties are modulated with the cell cycle. The involvement of erg currents in the setting of the resting potential of tumor cells is possibly due to the absence of classical inward-rectifying K^+ channels. Erg channels were also found in other tumor cells, like in cells of a microglia cell line (Zhou, W. et al., 1998). In a study of a variety of tumors of different histogenesis, HERG-like currents were found in the tumor cells but not in the normal parental tissues (Bianchi et al., 1998).

Neuroblastoma cells are blocked in the process of neuronal differentiation. This block can be overcome upon adhesion of the cell to extracellular matrix (ECM) proteins. These proteins bind to integrin receptors, thereby inducing signs of differentiation like neurite outgrowth. In cells of a murine and a human neuroblastoma cell line neuritogenesis was accompanied by a hyperpolarization of the resting potential by 10 to 20 mV due to an increased erg current amplitude (Arcangeli et al., 1993, 1996). The hyperpolarization as well as the neurite outgrowth could be blocked by PTX (Arcangeli et al., 1993, 1996) demonstrating that the ECM-induced response is mediated by G proteins.

In neuroblastoma cells the possible role of erg channels for spike frequency adaptation has been demonstrated (Chiesa et al., 1997). Upon a long-lasting depolarization of an excitable cell the evoked repetitive activity exhibits increasingly longer interspike intervals until no further action potential can be elicited. This phenomenon has been attributed to the activation of different types of K^+ currents such as the M current (Brown, 1988). In neuroblastoma cells the slow gating kinetics of erg channels are also well suited to mediate spike frequency adaptation (Chiesa et al., 1997; Schönherr et al., 1999). During successive action potentials, an increasing number of erg channels is activated because the interspike interval is too short to deactivate the erg current. Therefore, during a train of action potentials, a frequency-dependent accumulation of erg outward current occurs. Spike-frequency adaptation is abolished after erg channel block with WAY-123,398 (Chiesa et al., 1997).

Conclusion

The examples for endogenous EAG-like K^+ currents demonstrate that eag and erg channels may mediate a variety of physiological functions. Native elk currents have not been described so far. The contribution of HERG in repolarizing the cardiac action potential is the best studied physiological function of an EAG channel. Other examples for native eag and erg currents show that these currents are also involved in the setting of the resting membrane potential. In differentiated cells, a depolarization induced by an erg channel block is related to a distinct task, like contraction, O_2 sensing or hormone secretion. In undifferentiated and tumor cells, eag and erg channel expression is often related to the cell cycle.

Up to now, there exists a discrepancy between the abundance of *EAG* mRNA and the scarcity of EAG current recordings. This discrepancy is especially obvious in the rat brain where mRNA for all EAG channel subunits so far cloned has been detected (Saganich et al., 1999; Wulfsen et al., 2000). Whereas in clonal neuroblastoma cells native eag and erg currents have been recorded, the function of EAG subunits in normal nerve cells remains obscure. Reasons for the failure to detect endogenous EAG currents could be that EAG subunits interact with other K^+ channel α- or β-subunits, thereby masking their characteristic properties or that they are not functionally incorporated into the plasma membrane. The use of selective erg channel blockers has been shown to be an efficient method to detect and analyze native erg currents, and, hopefully, the discovery of selective eag and elk channel blockers will increase the number of examples for the physiological role of members of the EAG K^+ channel family.

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