“Disinactivation” of N-type Inactivation of Voltage-gated K Channels by an Erbstatin Analogue*

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In some A-type voltage-gated K channels, rapid inactivation is achieved through the binding of an N-terminal domain of the pore-forming α-subunit or an associated β-subunit to a cytoplasmic acceptor located at or near the channel pore using the ball-and-chain machinery (1–5). This inactivation involving the N terminus is known as N-type inactivation. Here, we describe an erbstatin (Erb) analogue as a small molecular inhibitor of the N-type inactivation in channels of Kv1.4 and Kv1.1+Kvβ1. We show that this inhibition of inactivation (designated as “disinactivation”) is potent and selective for N-type inactivation in heterologous cells (Chinese hamster ovary and Xenopus oocytes) expressing these A-type channels. In Chinese hamster ovary cells, Erb increased the inactivation time constant of Kv1.4 from 86.5 ± 9.5 to 150 ± 10 ms (n = 6, p < 0.01). Similarly, Erb increased the inactivation time constant of Kv1.1+Kvβ1 from 10 ± 0.9 to 49.3 ± 7 ms (n = 7, p < 0.01). The EC_{50} for disinactivating Kv1.1+Kvβ1 was 10.4 ± 0.9 μM (n = 2–9). Erb had no effect upon another A-channel, Kv4.3, which does not utilize the ball-and-chain mechanism. The mechanism of Erb-induced disinactivation was also investigated. Neither cysteine oxidation nor tyrosine kinase inhibition was involved. The results demonstrate that Erb can be used as a base structure to identify potent, selective small molecule inhibitors of intracellular protein-protein interactions, and that these disinactivators may offer another therapeutic approach to the treatment of seizure disorders.

The amino-terminal domains of the Shaker, Kv1.4, and Kv3.4 K channel α-subunits, and the Kvβ1 β-subunit underlie rapid inactivation in certain Kv channels (so-called N-type inactivation; Refs. 1, 2, 4, 5). Because short synthetic peptides encoding these N-terminal amino acids can induce rapid inactivation when applied intracellularly to noninactivating Kv channels (3, 4, 6), we reasoned that the protein-protein interaction between these N-terminal inactivation domains and their putative receptor, the cytoplasmic S4-S5 loop of the channel α-subunit (2), could be used as targets for drug discovery. Moreover, we reasoned that small synthetic organic molecules that disrupt this protein-protein interaction might also eliminate N-type inactivation (a phenomenon we designated as “disinactivation”) when applied to mammalian cells expressing the corresponding full-length channel subunits, and that further suppress aberrant neuronal excitability by keeping rapidly inactivating Kv channels open longer. We focused on the human Kv1.4 and Kv1.1 α-subunits and the Kvβ1 β-subunit primarily because these three polypeptides coassociate and colocalize in hippocampal circuits (7) that are frequently involved in seizure initiation and propagation in experimental animals and in humans. High-throughput screening strategies designed to search for small molecules that would achieve this kind of disinactivation have been presented previously (8).

We have previously reported (9) that N-type inactivation can be modulated by tyrosine phosphorylation and dephosphorylation. During our detailed studies, we have discovered rather unintentionally a novel effect of a compound known as erbastatin (Erb)1 analogue, methyl 2,5-dihydroxycinnamate (Fig. 1a; Refs. 10, 11). The results suggest that Erb may bind to the channel directly to affect the “ball-and-chain” mechanism and, thereby, the N-type inactivation. Because we used disinactivation (see above) to define the reduction or elimination of the N-type inactivation, agents like Erb are designated as “disinactivators.” The results in this report demonstrate that Erb or its analogues can be used as a base structure to identify potent, selective small molecule inhibitors of intracellular protein-protein interactions, and that these disinactivators may offer another therapeutic approach to the treatment of seizure disorders.

**EXPERIMENTAL PROCEDURES**

**Expression of Kv Channels in Chinese Hamster Ovary (CHO) Cells**—Human Kv1.1 and Kv1.4 cDNAs were inserted into a mammalian expression vector, pWE1, to yield pWE1/Kvs. The constructs were characterized by restriction enzyme mapping and DNA sequencing (deoxyribonucleotide chain termination method). CHOKI cells were transfected with pWE1/Kvs using a non-liposomal formulation, FuGENE 6 transfection reagent (Roche Applied Science). Cells expressing Kv channels were detected by co-transfecting cells with a fluorescence marker, the green fluorescent protein-encoding plasmid. To produce Kv1.1/Kvβ1 channels, a stable CHO cell line expressing Kv1.1 was transiently transfected with Kvβ1 cDNAs using FuGENE 6 transfection reagent.

**Expression of Kv Channels in Xenopus Oocytes**—For cRNA synthesis, in vitro transcription was carried out using a T3 mMESSAGE kit (Ambion) after linearization of the construct with NotI. Xenopus oocytes (stages V-VI) were injected with 46 nl of aqueous solution containing less than 10 ng of cRNA using a Drummond Nanoject II auto-nanoliter injector (Drummond Scientific Co., Broomall, PA). At or after 48 h of RNA injection, oocytes were tested using a two-electrode voltage-clamp for channel expression.

**Electrophysiology**—All experiments were performed at room temperature (22–23 °C) using the standard patch-clamp whole-cell re-

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Disinactivation of A-type Channels by Erbstatin Analogue

were considered to be significant at p < 0.01. Because of the
invariance of the peak currents measured in the absence of Erb and presence of Erb.

Solutions and Chemicals—For patch clamp, the pipette solution used in this study contained 145 mM KCl, 2 mM MgCl2, 10 mM HEPES, 10 mM EGTA, and 5 mM MgATP. The pH was adjusted to 7.4 with KOH. The bath solution was made from modified Hanks’ balanced salt solution (10-fold diluted, Invitrogen) and consisted of 5.4 mM KCl, 136.9 mM NaCl, 0.34 mM NaHPO4, 7 mM, 0.5 mM MgCl2, 6 mM K2HPO4, 0.41 mM MgSO4, 1.26 mM CaCl2, 10 mM HEPES, 11 mM glucose, and 0.01 g/liter phenol red. NaOH was used to adjust the pH to 7.3.

For Xenopus oocyte recordings, the electrodes were filled with 3 M KCl solution, with resistances ranging from 0.5 to 1.5 MΩ. The bath solution of pH 7.4 was an “ND96” containing 96 mM NaCl, 2 mM KCl, 1.8 mM CaCl2, 1 mM MgCl2, and 10 mM HEPES.

Erb (purchased from Calbiochem) was dissolved in Me2SO as a stock solution (50 mM). The final vehicle concentration was below 0.25%, at 0.34 mM NaH2PO4, 7H2O, 0.5 mM MgCl2, 6H2O, 0.41 mM MgSO4, 1.26 mM CaCl2, 10 mM HEPES, 11 mM glucose, and 0.01 g/liter phenol red. NaOH was used to adjust the pH to 7.3.

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Data Analysis—Current amplitude was measured online using a HEKA Pulse version 8.5 software. Mono-exponential fits in the HEKA Pulse Fit or Origin were applied to obtain activation, inactivation, and deactivation time constants ($\tau_a$, $\tau_i$, and $\tau_d$). Data were expressed as the mean ± S.E., and the paired Student’s t test was performed. Differences were considered to be significant at p < 0.05.

RESULTS

In the following text, we designate the compound methyl 2,5-dihydroxycinnaminate as Erb to distinguish it from other analogues in our company’s compound library. Our data indicated that Erb nearly abolished the N-type inactivation of a Kv1.4 channel expressed in CHO cells (Fig. 1, b–d), resulting in a drastic increase in the sustained current amplitude at all test potentials. In six cells, Erb (50 μM) increased the inactivation time constant of 86.5 ± 9.5 to 150 ± 10 ms (p < 0.01). The I/V plots in Fig. 1d clearly show that the peak currents measured in the absence (•, control) and presence (△) of 50 μM Erb are virtually the same. In contrast, the sustained current measured at the end of the depolarization pulses was drastically increased by Erb (▲ versus ○). Because the phenomenon of the fast closing and thus transient opening of the A-type K channels is known as “inactivation,” the disruption and reversal of the inactivation is designated here as disinactivation. Agents such as Erb that cause disinactivation are therefore designated as disinactivators. To rule out the possibility that host cells may play a role in the Erb-induced disinactivation, we have used both CHO cells and Xenopus oocytes in the following experiments. Because the results were very similar, only one set of data was used in some figures.

As mentioned above, there are several genes that encode the A-type K channels. The inactivation mechanisms of these A-type channels differ. The best known examples are the so-called N-type inactivation because the inactivation machinery involves some 20–50 amino acid residuals in the N terminus of the Kvα-subunits (12, 13). It is also well established that some Kvβ-subunits (such as Kvβ1), when co-expressed with certain Kv channels, can confer the N-type inactivation mechanism to some otherwise non-inactivating K channels such as the “delayed rectifier” type Kv1.1 (4, 14). Therefore, experiments were designed to test whether Erb would disinactivate these converted A-channels. As shown in Fig. 2b, when Kv1.1 and Kvβ1 were co-expressed in CHO cells (and in Xenopus oocytes), a mixture of inactivating and non-inactivating currents was recorded. When Erb was applied to the bath solution, the amplitude of both the peak and sustained currents was increased with an apparent slow-down of the inactivation. Erb reached its maximum disinactivation within 15 min after being applied to the bath. Similar to what happened with Kv1.4, Erb (50 μM) increased the inactivation time constant of Kv1.1 + Kvβ1 from 10 ± 0.9 to 49.3 ± 7 ms (n = 7, p < 0.01). Because of the difficulties in retaining the inactivation properties using mutated A-channels, we chose to test Erb on Kv1.1α-subunits expressed alone in CHO cells and Xenopus oocytes. When expressed alone, Kv1.1α-subunits form non-inactivating delayed rectifier-type channels. In this case, Erb had no effect upon the kinetics (data not shown).

The evidence shown so far suggests that Erb disinactivates...
Kv channels that bear the N-type inactivation mechanisms and does not affect the kinetics of the non-inactivating delayed rectifier K channels (such as Kv1.1). To test whether the Erb-induced disinactivation is specific only to the A-channels that exploit N-type inactivation, we performed experiments on another group (Kv4) of A-channels that inactivate without having a major N-type inactivation machinery in their \( \alpha \)-subunits (15, 16). Fig. 2, d and e show a representative Kv4 member, Kv4.3 channel current, recorded from a Xenopus oocyte. The currents inactivate by over 80\% during the 400-ms depolarization pulses. When Erb (up to 200 \( \mu \)M) was applied to the bath solution, neither the peak amplitude nor the inactivation kinetic was affected (\( n = 3 \)).

Hitherto we have provided evidence (see above) to suggest that Erb selectively disrupts the N-type inactivation of Kv1.4 and Kv1.1/Kv3.1 channels. In contrast, the delayed rectifier Kv1.1 alone or another A-type channel, Kv4.3, that does not follow the N-type inactivating scheme, is not affected by Erb. The N-type inactivation utilizes the so-called ball-and-chain mechanism (5, 17). The data suggest that Erb may interfere selectively with the ball-and-chain N-type inactivation. It is well known that N-type inactivation is prevented by oxidation of the cysteine residuals on the channel protein. This oxidation results in the formation of disulfide-bonds between the ball structure and the channel body, which immobilizes the ball and chain on the N terminus of the channel, thereby leaving the channel open without inactivation (18, 19).

To test whether the effect of Erb is by means of cysteine oxidation, we used two cysteine-specific oxidizing agents, 2,2'-dithiobis-5-nitropryidine (DTBNP) and chloramine-T (18). DTBNP (50 \( \mu \)M) virtually abolished the inactivation of Kv1.4 immediately after the agent reached the bath (in a matter of milliseconds). The effect of DTBNP could be reversed readily by the reducing agent dithiothreitol (DTT) (Fig. 3, a and b). CL-T at 500 \( \mu \)M also abolished the inactivation of Kv1.4 and was readily reversible by DTT as reported previously (Ref. 18 and data not shown).

When Erb was applied to the bath, however, the onset of its action on the channel inactivation was slower compared with that with DTBNP or CL-T (Fig. 3d). In the presence of Erb, DTT did not produce any effect upon the channel inactivation, suggesting that redox-regulation and the disulfide bond formation between the cysteine residuals are not involved in the Erb-induced disinactivation of A-type K channels.

It is noteworthy that, for some unknown reason(s), DTT alone does produce minor inhibitory effects on the current peak amplitude (Fig. 3, a and c). Moreover, preliminary site-directed mutation of the cysteine at position 7 to serine in the rat Kv3.1 polypeptide creates a subunit that induces rapid inactivation of Kv1.1 channels, but this inactivation is no longer sensitive to the effects of oxidants such as \( \text{H}_2\text{O}_2 \) (4). As a final control to ensure that the effects of the Erb analog disinactivator compounds (from our own library) were not due to redox modulation of this critical C7 residue, we coexpressed the Kv3.1C7S mutant with Kv1.1 in Xenopus oocytes. Application of an Erb analog disinactivator compound to
oocytes expressing this mutant subunit caused disina-
tivation similar to that of the wild-type channels. Thus the Erb
analog disinaactivator compound does not seem to disina-
tivate A-channels by oxidizing their N-terminals.

Because Erb is a known tyrosine kinase inhibitor and be-
cause tyrosine phosphorylation has been implicated in Kv
channel kinetics (20–23), we next performed experiments us-
ing a specific tyrosine phosphatase inhibitor and other nonspe-
cific but potent tyrosine kinase inhibitors to see whether the
tyrosine kinase pathway was involved in the Erb-induced K

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channel disinactivation. As shown in Fig. 4a, the tyrosine phosphatase inhibitor sodium orthovanadate alone (0.5 mM) had no effect upon the A-type voltage-gated K channel (Kv1.1+Kβ1). At the same concentration, sodium orthovanadate alone did not affect the inactivation of Kv1.4 either (not shown here). In the continued presence of sodium orthovanadate, the Erb-induced disinactivation was not affected (Fig. 4a), suggesting that the Erb-induced disinactivation may not involve a protein tyrosine kinase pathway. To further support this hypothesis, we have tested several other tyrosine kinase inhibitors that have different structures. These include genistein, tyrphostin 25, levendustin A, and herbimycin A. None of these potent tyrosine kinase inhibitors produced any Erb-like effects upon channel inactivation. These inhibitors not only have different structures compared with Erb but also work through different mechanisms to inhibit protein tyrosine kinases (e.g. compete with ATP, or their substrates, or both). As can be seen from Fig. 4b, the potent protein tyrosine kinase inhibitor levendustin A had virtually no effect upon channel inactivation.

Although Erb and vanadate have been shown to be very selective on tyrosine kinase pathway over the protein kinase C or protein kinase A pathway, we have performed some pilot experiments in the presence of a nonspecific protein kinase C and protein kinase A inhibitor, H7. As illustrated in Fig. 4c, H7 (20 µM) was applied both in the bath and intracellularly (included in the pipette solution). H7 alone did not have a significant impact upon channel inactivation. In the presence of H7, the Erb-induced channel disinactivation was not affected, which suggests that the protein kinase C or protein kinase A pathway may not be involved in the Erb-induced disinactivation.

**DISCUSSION**

In the present study, we have shown that Erb selectively interacts with the N-type inactivation of voltage-gated K channels, an effect we call disinactivation. It has also been demonstrated that the Erb-induced disinactivation is not mediated by oxidation or by means of a tyrosine kinase pathway. We propose that Erb may interfere with the channel inactivation machinery directly, and the effect might be either on the channel N-terminal “ball” peptide (involving the first 20 amino acids) or on the “receptor” site on the S4-S5 loop of the Kv channels (2). Accordingly, there might be at least three possible binding sites on the channel: the S4-S5 loop as the receptor site for the ball peptides, the α ball, and/or the β ball peptides per se. Given the fact that there is very little homology between the Kv1.4 N-terminal ball structure and the Kβ1 ball structure, the action site is highly likely to be located near the receptor site on the S4-S5 loop of the Kv α-subunits. Binding of a small molecule disinactivator such as Erb to the ball peptides might reduce the flexibility of the ball-and-chain machinery, which makes it impossible for the ball peptides to reach their binding sites at the S4-S5 loop. Alternatively, binding of Erb to the S4-S5 loop alone may prevent the ball peptides from interact-

ing with this intracellular loop, leaving the gate either fully open or “ajar.”

The Erb-induced disinactivation on the voltage-gated K channel can prolong the opening of these K channels, thereby reducing the neuronal excitation and neurotransmitter releases. Agents that mimic this type of disinactivation are designated as disinactivators here. We reason that disinactivators are the first class of small molecules that interfere with the protein-protein interaction for the ball-and-chain in N-type inactivation. These disinactivators, therefore, would be useful for treating disorders such as epilepsy and stroke. Furthermore, we found that those Erb analog disinactivators mimic the effects of Erb upon the N-type inactivation and are efficacious in two in vivo seizure models: the maximum electric shock-induced seizures and the picrotoxin-induced seizures. The striking notion is that most of the currently marketed anticonvulsant drugs worked only in one of the seizure models. Therefore, small molecule K channel disinactivators represent a new class of antiseizure drugs, and these drugs can be expected to be more efficacious and to have less severe side effects.

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