Molecular properties of potassium channels

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Summary: *The paper describes the molecular pharmacology and biochemistry of three types of K^+ channels, the calcium-activated potassium channels, ATP-regulated potassium channels and voltage-sensitive potassium channels.*

Zusammenfassung: *Molekulare Eigenschaften von Kalium Kanälen*

In der vorliegenden Arbeit werden die Pharmakologie und Biochemie von drei verschiedenen K^+-Kanälen beschrieben: den Calcium-aktivierten Kalium-Kanälen, den ATP-regulierten Kalium-Kanälen sowie den Spannungs-sensitiven Kalium-Kanälen.

Key words: *Ion channels · Potassium channels, ATP-regulated, calcium-activated, molecular properties, voltage-sensitive*

1. Ca^{2+}-activated K^+ channels

The calcium activated potassium channel (Ca^{2+}-activated K^+ channels) has been the first one among K^+ channels for which a good molecular pharmacology was established.

Mammalian myotubes in culture contract spontaneously. In order to contract spontaneously they, of course, have to generate spontaneous action potentials. In order to generate spontaneous action potentials, afterhyperpolarization (ahp) is required and it is during this hyperpolarization phase which works as a pace-maker that the sodium channel that has been activated and then inactivated during the first action potential is reactivated then allowing the generation of a new action potential. The Ca^{2+}-activated K^+ channels are activated by a combination of variations of membrane potential and variations of internal calcium concentrations. The Ca^{2+}-activated K^+ channel that is described here is sensitive to the toxin apamin (Fig. 1) [1—4]. This toxin from bee venom consists of 18 amino-acids [5]. Its active site is made of 2 arginines [6, 7]. The ahp which is responsible for the pace-making activity and which is associated with the activity of Ca^{2+}-activated K^+ channels is blocked by apamin concentrations in the 1—10 nmol/l range (Fig. 1). The toxin blocks Ca^{2+}-activated K^+ channels involved in the ahp but it does not block the other class of (big) Ca^{2+}-activated K^+ channels [3] (BK channels ≈ 250 pS.). The big channels are blocked by TEA (tetraethylammonium), but the ahp is not blocked by TEA [3]. The big channels are also blocked by a toxin recently discovered by Miller et al. — charybdotoxin [8] — but the ahp is not affected by charybdotoxin. In the skeletal muscle cell the pace-maker channel which is blocked by apamin is not blocked by TEA or charybdotoxin. In contrast we have found recently [9] with an aortic cell line having a repetitive activity that the ahp which is responsible for this repetitive activity is blocked by charybdotoxin and not by apamin.

One very interesting thing about the apamin-sensitive Ca^{2+}-activated K^+ channel in muscle concerns the transformation

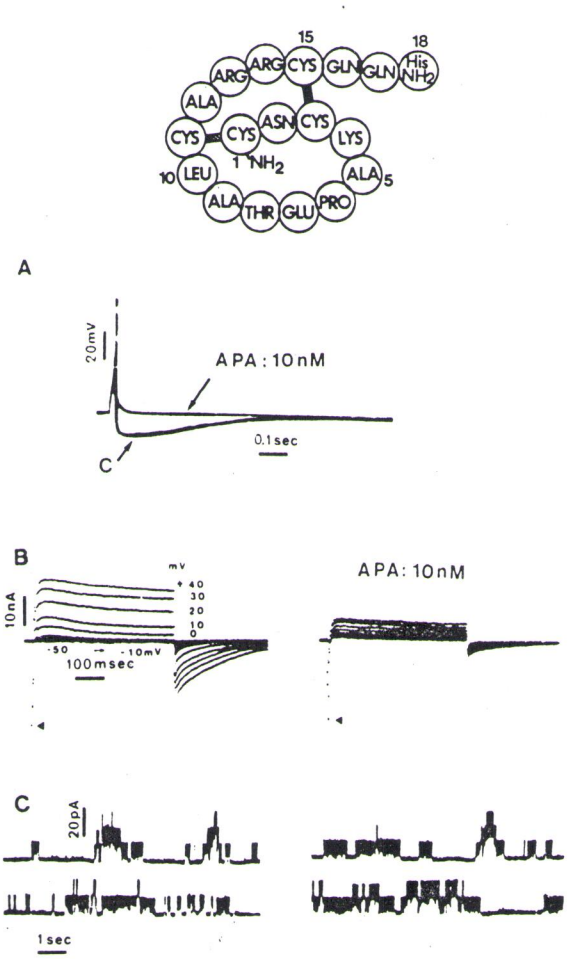

Fig. 1: Upper part: The structure of apamin.
A: ahp in the control (C) is blocked by apamin (APA).
B: Voltage-clamp analysis of the effect of apamin on rat myosacs. Families of membrane currents associated with different step depolarizations from 90 mV. Experiment done in 20 mmol/l TEA.
C: Single channel recordings of the Ca^{2+}-dependent K^+ channel at +30 mV. Left: Control. Right: Absence of effect in 10 nmol/l apamin.

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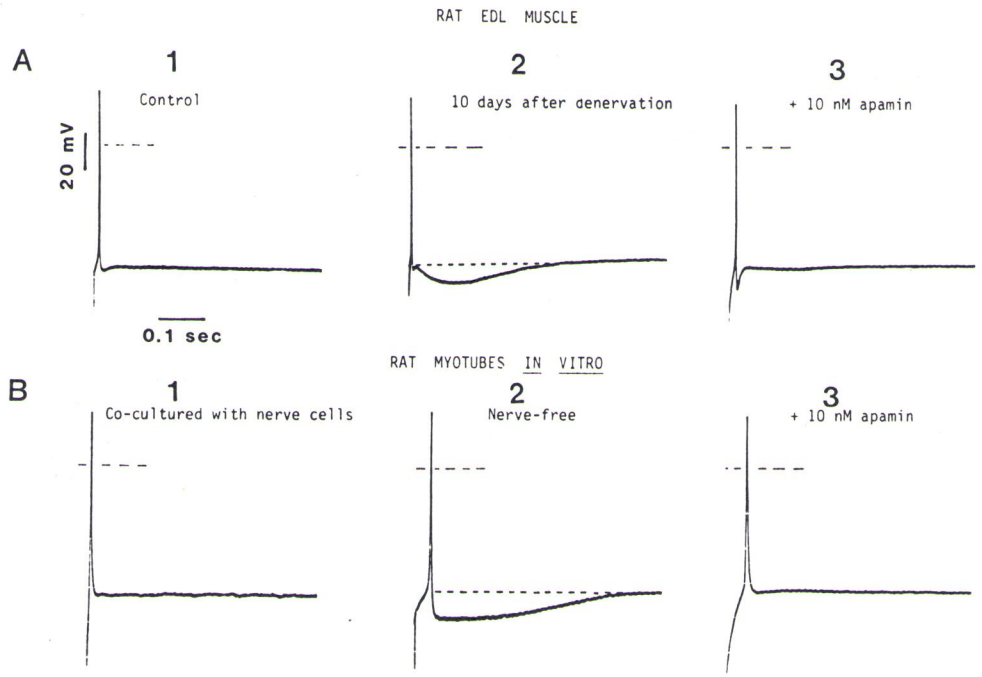


Fig. 2: Effects of innervation **(B)** and denervation **(A)** on the expression of the apamin-sensitive Ca^{2+}-activated K^+ channel.

of its properties during the course of innervation. When the myotube is not innervated it contracts spontaneously and this contraction is essential for survival. Of course, later in developement the skeletal muscle cell will be innervated and then no one wants it to contract spontaneously anymore. At that stage contractions should only occur under the order of the nerve. Several things do happen in this muscle cell during innervation in order to change its electrical phenotype. First of all, there is a change in the resting potential corresponding to an hyperpolarization. The reason for this hyperpolarization is to bring the resting potential farther from the threshold of the generation of the action potential i.e. from the threshold of activation of the sodium channel. The second thing that one would expect is the disappearance of the apamin-sensitive channel which is an essential element of the repetitive electrical activity. This is exactly what happens [10].

If one keeps rat myotubes in vitro and innervate them by co-culture with spinal cord cells one observes after a while that the action potential is no more followed by an ahp [10] (Fig. 2). In other words, as predicted, the innervation of the skeletal muscle cells has repressed the expression of the apamin-sensitive K^+ channel. Inversely, if one takes normal muscle it does not have spontaneous contractions nor repetitive activity, and it lacks any ahp following the action potential. Ten days after denervation of this muscle, the ahp appears and is completely blocked by apamin [10] (Fig. 2). Then the clear message that comes from these data is that when the muscle is not innervated the apamin-sensitive Ca^{2+}-activated K^+ channel is expressed. When the muscle is innervated that channel disappears. When the muscle is denervated the Ca^{2+}-activated K^+ channel reappears.

All these observations led our attention to a frequent human muscle disease, i.e. myotonic muscle dystrophy or Steinert disease. Patients have myotonic discharges and cannot easily relax their muscles. The normal innervated human muscle like the rat muscle, when it is innervated, fails to express the apamin-sensitive Ca^{2+}-activated K^+ channel [11]. In Steinert disease, the muscle, although it is normally innervated, expresses, as expected, the Ca^{2+}-activated K^+ channel identified as an apamin receptor. Also muscles of patients with Steinert disease are known to be more depolarized than those of normal muscles [12]. This is probably the molecular explanation of the myotonic symptoms in the disease. It seems that in Steinert disease there is impairment not only in the muscle but also in the relationship between nerve and muscle [11].

Apamin-sensitive channels are not only present in skeletal muscle. They are also present in smooth muscles where they participate to contraction. They are also present in the nervous system and ^{125}I-apamin has been used to locate the apamin receptor by autoradiography throughout the nervous system and at different steps of brain differentiation [12]. The apamin receptor is expressed very early during brain ontogenesis — earlier actually than calcium channels visualized as calcium channel blocker receptors or the sodium channels visualized as tetrodotoxin receptors. It is of course important to know whether these receptors correspond to functional Ca^{2+}-activated K^+ channel. One way to have the answer is to measure deoxyglucose consumption in the different parts of the brain after apamin injection [13]. If apamin blocks Ca^{2+}-activated K^+ channels, this blockade will change the rhythm of firing in different parts of the brain and this in turn will change deoxyglucose consumption. This is an indirect way to see whether apamin receptors are associated with channel activity. For example upon injection of apamin in very low concentrations — at which there are no visible effects on the animal — it becomes obvious that the glucose consumption increases tremendously in the auditory cortex, an area which is rich in apamin receptors. In general the apamin receptors and the consumption of glucose have similar localizations [13].

What do we know about the molecular properties of this apamin-sensitive channel? The activity of the apamin-sensitive K^+ channel can be recorded in neuroblastoma cells. Fig. 3 shows that it is a small channel with a conductance of about 9 pS. What do we know about the structure of the channel protein? Although apamin binds very tightly to its receptor, with a K_D of about 20 pmol/l [2, 14], solving the structure of the Ca^{2+}-activated K^+ channel that is blocked by apamin is difficult because the number of apamin binding sites is very low in practically all cells we have worked with. That makes, of course, the purification extremely difficult. Radiation-inactivation gave a molecular weight of about 250 000 and the main polypeptide chain that is affinity labelled with the toxin has a M_r of about 30 000 [15, 16]. How-

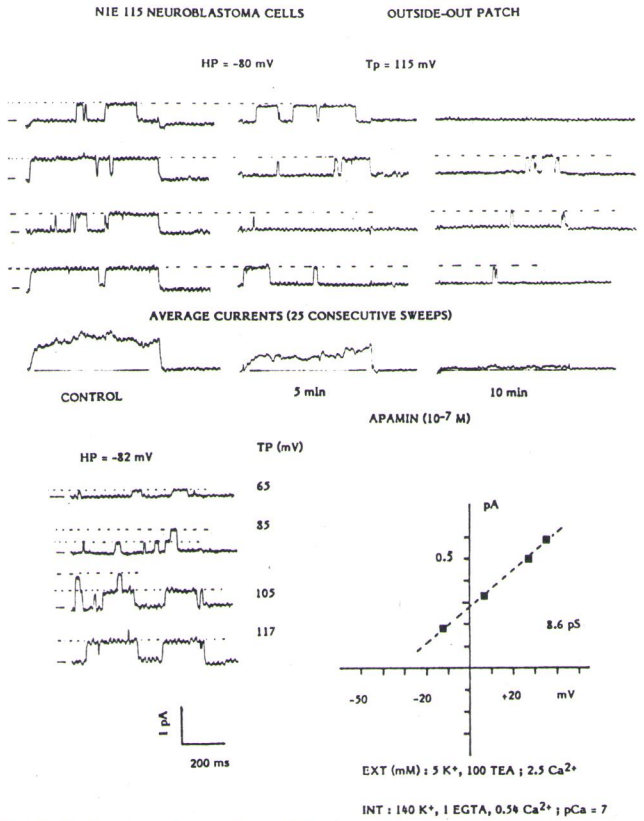


Fig. 3: Single channel recordings of the apamin-sensitive Ca^{2+}-activated K^+ channel in neuroblastoma cells.

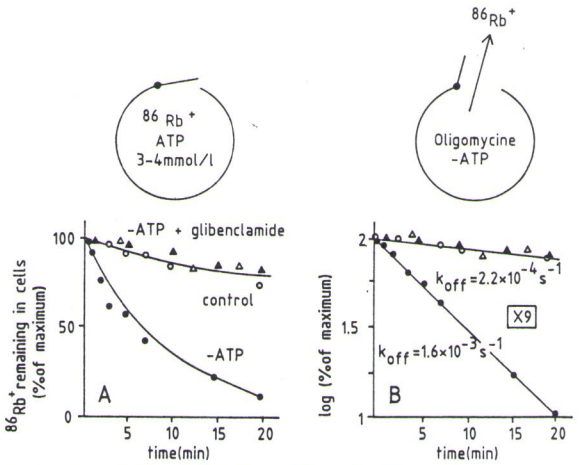


Fig. 4: Kinetics of $^{86}Rb^+$ efflux from RINm5F, effects of ATP depletion on $^{86}Rb^+$ efflux and blockade of the stimulated $^{86}Rb^+$ efflux by glibenclamide.

ever, it appears now that there may be a least another polypeptide chain at a molecular weight 90 000 [17].

What is the calcium sensitivity of this pace-maker channel? The answer has been obtained with a cell for which we have discovered that it over-expresses the apamin-sensitive Ca^{2+}-activated K^+ channel. This cell is the pheochromocytoma cell, PC12. It produces about 100 times more receptors for apamin than any other cell types [18]. With this type of cell one can relate the activity of the apamin-sensitive channel to the intracellular Ca^{2+} concentration. At 10^{-7} mol/l $[Ca^{2+}]_{in}$, the channel is not activated but if the internal concentration increases only to 3×10^{-7} mol/l the channel is then fully activated. This Ca^{2+}-activated K^+ channel is activated at very low $[Ca^{2+}]_{in}$ concentrations and the dose-response curve for the internal Ca^{2+} concentration is very steep with a Hill coefficient of more than 3.

The existence of an apamin-like molecule endogeneous to the brain [19] is one of the important aspects of the apamin-sensitive Ca^{2+}-activated K^+ channel.

2. ATP-regulated K^+ channels

This class of K^+ channels is regulated by internal ATP concentrations. At high ATP concentration the channel is closed. When the concentration of ATP becomes lower the channel is open. Therefore, a low ATP concentration will give an hyperpolarization, whereas a higher ATP concentration will lead to the closing of the potassium channel and lead to depolarization [20—23].

This channel has been recently shown to be very important especially for β-cells. When a β-cell is perfused with glucose it generates spontaneous action potentials. The β-cell has a normal potential near —70 mV. As soon as it is perfused with glucose it depolarizes slowly and then the depolarization reaches the threshold for activation of calcium channels. Then the cell fires calcium action potentials, calcium gets inside of the cell and insulin is released. The interesting thing is that not only glucose has this effect but also a class of pharmacological important molecules, the sulfonylureas, which have now been used for more than 20 years for the treatment of diabetes of type 2. Tolbutamide or any other sulfonylurea produce the same electrical effects as glucose perfusion i.e. a slow depolarization leading to generation of calcium action potential [24]. The easiest interpretation is the following for the glucose effect. When the cell is perfused with glucose, the intracellular ATP concentration increases, an increase of the ATP concentration will block the ATP-regulated potassium channels and then of course depolarization will occur. All these results taken together suggest that there is a link between glucose and tolbutamide or sulfonylureas in general and that glucose and sulfonylureas have, at least indirectly, the same type of target.

We have used the following strategy to show that sulfonylureas are blockers at ATP-regulated K^+ [25, 26]. In normal insulinoma cells, the intracellular ATP concentration is 3 to 4 mmol/l. These cells were loaded with $^{86}Rb^+$ then depleted of ATP with oligomycin. After treatment of the cells with oligomycin, the ATP concentration dropped drastically, the ATP-regulated potassium channel opened and $^{86}Rb^+$ efflux occurred (Fig. 4). Sulfonylureas are very potent blockers of ATP-dependent potassium channels measured by this technique (K_d = 0.06 nmol/l for glibenclamide). Glibenclamide is a blocker of the ATP-regulated potassium channel that is more potent than tetrodotoxin for the sodium channel or more potent than 1,4-dihydropyridines for the calcium channel.

Results found by flux techniques have been verified by patch-clamp techniques [26] (Fig. 5). We have then used tritium labelled glibenclamide and have identified the sulfonylureas receptors. There is an impressive correlation for a whole series of drugs of the sulfonylurea family between the binding and the blockade (Fig. 6). This observation seems to provide enough evidence that the receptor of sulfonylureas is really closely linked to the ATP-regulated potassium channel [26].

We wanted to know whether these ATP-regulated potassium channels that are the targets of the very important anti-diabetic drugs could be regulated by hormones which could themselves play a role in the secretion of insulin by the pancreas, and our interest was attracted by an hormone called galanin. This is a 29 amino-acid hormone which, when applied to the pancreas, decreases insulin secretion. We have shown [27] that galanin opens ATP-regulated potassium channels (and therefore decreases insulin secretion), while sulfonylureas block ATP-regulated potassium channels (and therefore increase insulin secretion) [27].

Dose-response curve measured with the $^{86}Rb^+$ efflux assay are shown in Fig. 7.

Clearly ATP-regulated potassium channels and their regulation might be involved in diabetes of type 2.

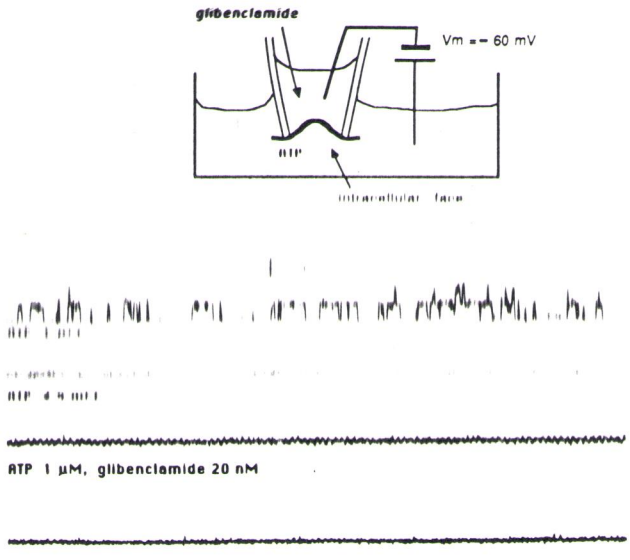
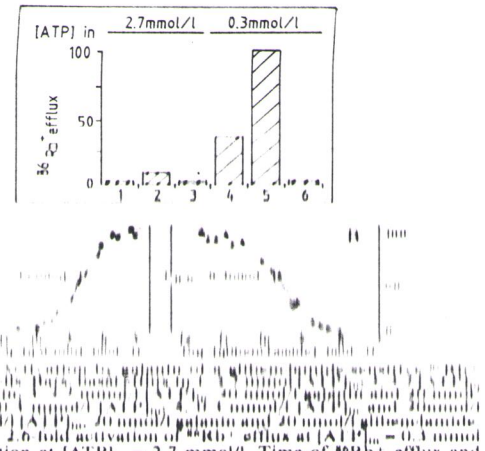


Fig. 5: Single channel currents recorded from inside-out patches of RINm5F cells. Membrane potential at −60 mV. ATP-regulated K^+ channels are opened at low $[ATP]_{in}$ concentrations and could be blocked at high (2.5 nmol/l) $[ATP]_{in}$ concentrations or by glibenclamide or glisopexide.



and a 4-fold activation at $[ATP]_{in}$ = 2.7 mmol/l. Time of $^{86}Rb^+$ efflux and inhibition by glibenclamide of this ^{86}Rb-activated efflux. Time was 1 min. Experiments were carried out in duplicate. **Lower part:** Dose-response curves of activation by galanin of ATP-sensitive $^{86}Rb^+$ efflux and inhibition by glibenclamide. Time of $^{86}Rb^+$ efflux was 1 min. $[ATP]_{in}$ depletion was for 20 min (then $[ATP]_{in}$ = 0.4 mmol/l). Experiments are done in duplicate. **A:** Activation of $^{86}Rb^+$ efflux measured in the presence of increasing concentration of galanin. **B:** Inhibition of $^{86}Rb^+$ efflux in the presence of 20 nmol galanin and increasing concentrations of glibenclamide.

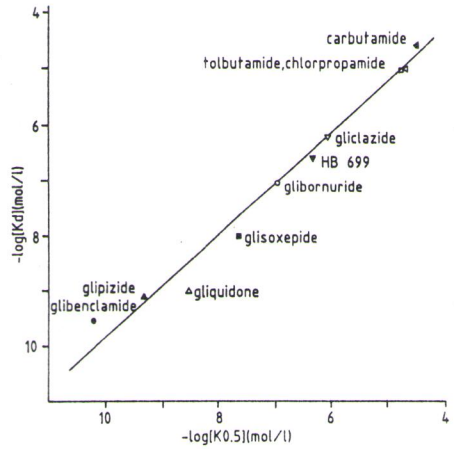


Fig. 6: Correlation between inhibition of various hypoglycemic drugs of specific [^{3}H]glibenclamide binding and of $^{86}Rb^+$ efflux. K_d = half-inhibition of ATP-sensitive rate of $^{86}Rb^+$ efflux.

The ATP-regulated potassium channel is not only present in β-cells but also in cardiac cells [28, 29]. The properties of the sulfonylurea receptors associated with the ATP-regulated potassium channels and cardiac cell are the same in biochemical terms as they are in β-cells [29]. ATP-regulated potassium channels may be present in neurons. There are glucose sensing neurons in the hypothalamus which control appetite and they may work by mechanisms similar to the one of the β-cell. Moreover one immediately thinks of the role of ATP-regulated potassium channels in ischemia of the brain (as well as of the heart [30]).

3. Voltage dependent K^+ channels

There is a large variety of voltage-dependent potassium channels. However up to recent years there was really no potent pharmacological tool to study them. The usual tools were TEA or 3,4-aminopyridine but these drugs act at high concentrations and are not completely selective. The situation has recently changed and one has new tools to study these channels.

We have been actively working on a bee venom peptide called mast cell degranulating peptide (MCD) [5] because it degranulates mast cells. It is a 22 amino-acid peptide which when injected intracerebroventricularly is tremendously neurotoxic [31, 32]. On intracellular injection of MCD one sees hippocampal θ rhythm appearing in the rat which is associated with alert immobility [31]; with higher doses of the peptide, epileptiform seizures and convulsions appear [31]. Application of MCD to hippocampus slices produced long-term potentiation [33]. Long-term potentiation is associated to arousal, learning and memory. This MCD peptide blocks one type of voltage-dependent potassium channels [34].

The MCD peptide receptor has been identified in brain membranes (K_D of about 100 pmol/l) and by quantitative autoradiography. MCD peptide receptors are present in most brain areas [35, 36].

Dendrotoxins are another class of snake toxins that block voltage-sensitive potassium channels [37]. These toxins have sequence homologies with trypsin inhibitors but not with the MCD peptide and they facilitate neurotransmitter release [37]. A number of recent results obtained in different laboratories show that these toxins block one type of potassium channel [37].

We have shown that the voltage-dependent potassium channel protein has two types of receptors, one for the MCD peptide, one for the snake venom peptide dendrotoxin and that these receptors are in allosteric interaction [36], (Fig. 8). MCD peptide binding is very strongly antagonized by dendrotoxin I in hippocampus [36].

The same protein with a same molecular weight of 72 000 is labelled in affinity labelling experiments both by the snake toxin and by the bee venom toxin MCD [38] (Fig. 9). Receptors for these toxins have now been completely purified [39]. They co-purify and we have confirmed that the main protein component has a molecular weight of 72 000. This

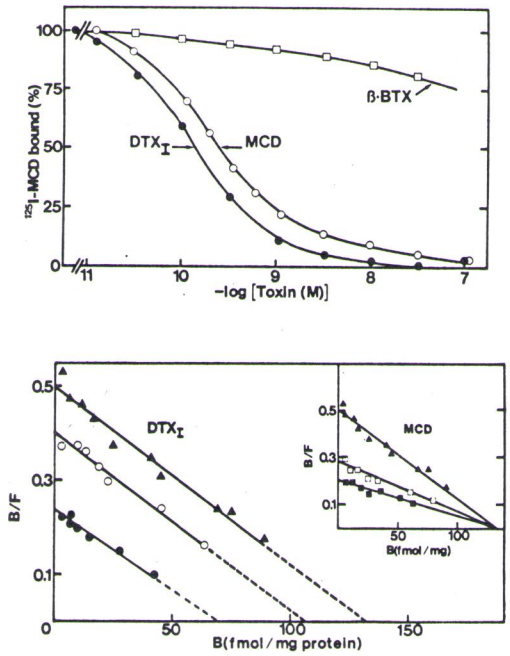


Fig. 8: Scatchard analysis of saturable binding to synaptosomal membranes. Inhibition by DTX_I. Synaptic membranes (150 µg protein/ml) were incubated with various concentrations of ^{125}I-MCD (1—200 pmol/l). Main panel: DTX_I was added at concentration (nmol) 0 (▲), 0.1 (○) and 0.32 (●). Inset: MCD was added at concentration (nmol) 0 (▲), 0.25 (□) and 0.5 (■). Specifically bound ^{125}I-MCD was quantified for duplicate samples and the Scatchard analysis of the free (F) and bound (B) ^{125}I-MCD concentrations were calculated.

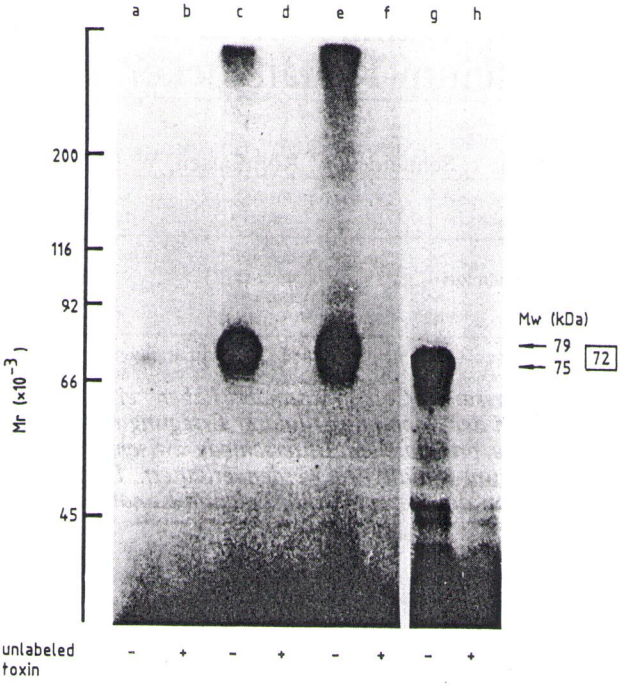


Fig. 9: Specific cross-linking (0.5 mg/ml dimethylsuberimidate) of ^{125}I-MCD (g) and ^{125}I-DTX (c and e) to synaptic membranes. Labelling was completely protected by unlabelled MCD and DTX. After Correlation for the M_r of the grafted toxins, the M_r of the receptor protein appears to be of 72 000.

protein is actually heterogeneous and may contain different highly homologous peptides corresponding to K^+ channels with slightly different biophysical properties of conductance and activation and inactivation kinetics [40]. This M_r is similar to the molecular weight of potassium channels cloned from Shaker mutants in Drosophila (70 000) [40, 42].

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ISSN 0004-4172

ARZNEIMITTEL FORSCHUNG

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Ionenkanäle: Struktur, Regulation und klinische Relevanz

22. Deidesheimer Gespräch 23./24. April 1988

39 (I), 115–186, Jan. 1989 1a

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DRUG RESEARCH®

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Publikationsorgan der Paul-Ehrlich-Gesellschaft für Chemotherapie

Begründer / Founder: Dr. Dr. Werner Saenger †

Anschrift der Redaktion / Editorial Office

Viktor Schramm

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Sekretariat / Secretary's office: Waltraud Frey

Lektorat / Readers' Department:
Irmgard Fränkel, Dietmar Glasauer

Verlag / Publisher

Editio Cantor
Verlag für Medizin und Naturwissenschaften GmbH
D-7960 Aulendorf (Fed. Rep. of Germany)

Arzneim.-Forsch./Drug Res. Band/Vol. 39 (I)
Seite/Page 115—186 · Januar 1989

Printed in the Federal Republic of Germany ·
ISSN 0004-4172

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