VOLTAGE-GATED ION CHANNELS AS DRUG TARGETS (METHODS AND PRINCIPLES IN MEDICINAL CHEMISTRY) pdf

1: Voltage Gated ion Channels: Targets for Anticonvulsant Drugs | BenthamScience

Further chapters cover genetic and acquired channelopathies, before the book closes with a look at safety issues in ion channel drug development. For medicinal and pharmaceutical chemists, biochemists, molecular biologists and those working in the pharmaceutical industry.

This article is distributed under the terms of an Attributionâ€"Noncommercialâ€"Share Alikeâ€"No Mirror Sites license for the first six months after the publication date see http: This article has been cited by other articles in PMC. Ion channels are well recognized as important therapeutic targets for treating a number of different pathophysiologies. Historically, however, development of drugs targeting this protein class has been difficult. Several challenges associated with molecular-based drug discovery include validation of new channel targets and identification of acceptable medicinal chemistry leads. New, functional, high throughput screening HTS strategies developed to identify tractable lead structures, which typically are not abundant in small molecule libraries, have also yielded promising results. Automated cell-based HTS assays can be configured for many different types of ion channels using fluorescence methods to monitor either changes in membrane potential or intracellular calcium with high density format plate readers. New automated patch clamp technologies provide secondary screens to confirm the activity of hits at the channel level, to determine selectivity across ion channel superfamilies, and to provide insight into mechanism of action. The same primary and secondary assays effectively support medicinal chemistry lead development. Together, these methodologies, along with classical drug development practices, provide an opportunity to discover and optimize the activity of ion channel drug development candidates. A case study with voltage-gated sodium channels is presented to illustrate these principles. Introduction Ion channels are important drug targets because they play a crucial role in controlling a very wide spectrum of physiological processes Hille, , and because their dysfunction can lead to pathophysiology Ashcroft, Given the strong historical precedent that exists for discovering and commercializing successful drugs that modulate the activity of voltage-gated sodium, calcium, or potassium channels, or ligand-gated ion channels, new generations of therapeutic agents are expected to result from targeting this protein family. Early ion channel drug discovery used classical pharmacological approaches, in which profiling in animal models, designed to simulate human disease states, was used to optimize compound activity, even if the nature of the molecular target was unclear. Serendipity, insight, and brute force effort drove these drug discovery efforts and resulted in a number of notable successes including successful therapies and discovery of research tools that have been invaluable in mapping out signaling pathways, purifying channel proteins, and characterizing gating mechanisms, all of which has sustained the present era of ion channel drug discovery Garcia and Kaczorowski, With the advent of a more complete understanding of cellular physiology and identification of the molecular components that constitute individual channel types and control their function, researchers are now focusing on a molecular-based strategy to identify drugs targeting this protein class. The molecular approach has been significantly strengthened by the advent of new technologies, including high throughput screening capabilities and automated electrophysiology. Despite these advances, the discovery and development of new ion channel drug candidates remains an arduous task. Significant challenges exist in the validation of new targets, which may be hindered by complex and potentially species-specific physiology Yu and Catterall, , difficulties in discovering acceptable small molecule leads, and the lack of biomarker and target engagement strategies to validate that drug exposure in patients is sufficient to differentiate negative from failed clinical trails. Each of these challenges is addressed in more detail in the remainder of this article, using examples from a drug discovery effort on voltage-gated sodium channels. Identification and Validation of Ion Channel Targets Drug discovery and development is a costly and time consuming process which, unfortunately, often meets with limited success. Issues that contribute to program failure include toxicity, due to the interaction of a development candidate with unrelated channels or other proteins e. An essential route to increased success in ion channel

drug discovery is rigorous application of traditional and novel in vitro and in vivo target validation approaches, including genetic and pharmacological validation studies, expression profiling, and altering channel expression in model systems. Improvements in the target identification and validation stage can, arguably, have the greatest overall impact on ion channel drug discovery efforts. Human genetics and gene ablation studies in rodents have identified a number of new ion channel targets e. Ashcroft, ; Lifton et al. In addition to traditional knockout techniques, modulation of channel expression by regulation of promotor activity, siRNA technology, or the employment of dominant-negative interference strategies can be used to aid in the validation of novel targets. As an example of human genetic validation, recent evidence has pointed to Nav1. The syndrome of Congenital Indifference to Pain has been linked to nonsense mutations in Nav1. These individuals have a complete inability to sense pain, and yet they appear normal in all other respects, including intelligence, physical development, motor and autonomic reflexes, and sensation with the exception of the sense of smell. Additionally, several human gain of function mutations have been identified in Nav1. Interestingly, the human loss of Nav1. Given the possibility of compensatory changes in genetically derived disease models, the most convincing target validation is derived from pharmacological proof of concept in an animal model reflecting human physiology. Such validation can be obtained through use of existing small molecule channel modulators, peptide neurotoxins, or antibodies specifically developed to inhibit channel function. Specific examples of target validation using existing drugs lidocaine, tricyclic antidepressants or peptides Ziconotide and GxTX are discussed below. Systemic administration of the local anesthetic lidocaine is approved for the treatment of neuropathic pain Priest and Kaczorowski, At clinically used concentrations, block of Nav1 channels appears to be the only mode of action of this agent. Similarly, tricyclic antidepressants, such as amitriptyline, which are efficacious in treating neuropathic pain, possess a broad spectrum of pharmacological activities including inhibition of Nav1 channels. A comparison between therapeutic efficacy and ability to inhibit Nav1. Tricyclic antidepressants were potent sodium channel inhibitors and their potency in binding to the inactivated state of Nav1. In contrast, antidepressant serotonin reuptake inhibitors that are not effective in treating post-herpetic neuralgia or diabetic neuropathy were weaker inhibitors of Nav1. These data suggest that inhibition of voltage-gated sodium channels may contribute to the anti-hyperalgesic efficacy of tricyclic antidepressants and is further support for targeting sodium channels to treat chronic pain with more potent and selective inhibitors. Another example of pharmacological validation comes from the use of peptides, such as Ziconotide, a synthetic analogue of a peptide contained in cone snail venom, and a potent blocker of the N-type voltage-gated calcium channel, Cav2. Ziconotide was developed clinically as a treatment for intractable pain by intrathecal administration. In vivo pharmacological results with Ziconotide strongly support the hypothesis that a systemic small molecule inhibitor of Cav2. Since peptidyl modulators of ion channels are abundant in venoms, they are rich sources for reagents useful in proof of concept studies. In addition, small molecule natural product channel modulators, including indole diterpene blockers of high conductance, calcium-activated potassium channels KCNMA1 , have been used as probes in target validation studies Garcia and Kaczorowski, Lead Identification and Characterization The most challenging aspect of ion channel drug discovery may be the identification of an appropriate, small molecule drug lead with desirable chemical properties that qualify it for exploration by medicinal chemistry MacCoss and Baillie, This is a key element in successful ion channel preclinical drug development. Ion channels have traditionally been considered difficult targets to engage in high throughput functional screening formats, and large scale screening campaigns have often yielded a paucity of potent, selective hits. The scarceness of acceptable ion channel leads may derive from the long-standing emphasis within the pharmaceutical industry on programs directed at G proteinâ€”coupled receptors, kinases, and other enzymes, leading to biased sample collections. Implementation of reliable and informative counter-screens for likely off-target activities is essential for meaningful hit assessment and lead prioritization to ensure that resources are not wasted in pursuing nondevelopable chemical structures. Recent introduction of fluorescent, cell-based screening technologies has enabled dependable HTS and ultra high throughput screening UHTS paradigms, allowing

screening of libraries consisting of millions of compounds in a timely, cost effective manner, and thereby allow detection of true lead structures with adequate initial potency, selectivity across ion channel superfamilies, and defined mechanisms of action. In one general configuration, HTS assays can be instituted for many different types of ion channels by establishing cell lines heterologously expressing the target in a context where changes in the activity of the channel of interest can affect the cellular plasma membrane potential. Potential sensitive fluorescent dyes can then be used to monitor changes in membrane potential of such cells grown in high density, multiwell format plates during screening procedures Gonzalez and Maher, Detection of an active compound is achieved if addition of test compound causes a corresponding change in membrane potential. This strategy works well to identify sodium or potassium channel modulators, and such paradigms can be used to screen for ligand-gated ion channel modulators, as well. Identification of both channel inhibitors and channel openers can be accomplished using this general screening method Garcia et al. For detecting voltage-gated calcium channel effectors, a similar approach can be adopted, except that fluorescent dye indicators are employed to monitor the concentration of intracellular calcium. Cotransfection with an inwardly rectifying potassium channel, together with the controlled variation in extracellular potassium concentration, has been used to control cellular membrane potential, in order to establish the most sensitive and mechanistically meaningful assay configuration Xia et al. All of these screening formats are amenable to application of ultrahigh throughput automation strategies. Until recently, the characterization of screening hits using manual voltage clamp techniques was slow and tedious, because of the low throughput inherent to this technique. Several different platforms are commercially available with specific features determining their optimal application, from specializing in high throughput analysis to more quantitative measurements of channel activity using complex voltage protocols Priest et al. Hopefully, automated patch clamp technologies will soon be adapted to UHTS requirements, enabling a new set of UHTS approaches toward finding novel ion channel modulators. Presently, the combination of biochemical and biophysical approaches is needed to identify useful lead structures. Together, these strategies, along with more classical drug development techniques, provide a means for discovering and optimizing the activity of potential ion channel drug development candidates for almost any member of the various ion channel super families. Discovering Inhibitors of Voltage-gated Sodium Channels As a way of illustrating the issues related to ion channel drug discovery outlined above, the remainder of this article will describe a case study focusing on the identification of voltage-gated sodium channel inhibitors to treat chronic neuropathic pain. Treatment of pain is a serious medical issue and there is a major effort in the pharmaceutical industry to develop new therapies for this condition. It is clear that voltage-gated sodium Nav1 channels play a key role in the origination and propagation of sensory nerve action potentials necessary for pain signaling. Local applications of nonsubtype-selective sodium channel blockers, such as novocaine, provide complete pain relief through conduction block. However, this approach to pain relief is limited to very few applications, such as dental procedures, since sodium channels are also vital to conduction in the heart, CNS, skeletal muscle, and nonnociceptive sensory neurons. The Nav1 super family is comprised of 10 members Yu and Catterall, Seven of these subtypes, Nav1. This limited expression pattern makes these subtypes attractive targets for the development of novel analgesic agents. However, their relative contribution to pain signaling, and specifically to neuropathic pain signaling, is unclear and may vary with different etiologies and sensory qualities of pain. In the absence of molecular selectivity for one Nav1 subtype, it is possible to specifically target Nav1 channels in a given conformational state while preserving sodium channelâ€”dependent impulse conduction. This type of state-dependent inhibition is the basis for the therapeutic window seen with sodium channel blocking anticonvulsants and antiarrhythmics, such as lamotrigine and lidocaine. This mechanism of inhibition favors binding in rapidly firing or partially depolarized tissues. Neuropathic pain should be sensitive to this inhibitory mechanism, since it is thought to arise from injury-induced areas of depolarizations, a hypothesis that is supported by the clinical efficacy of lidocaine administered systemically at subanesthetic doses. Moreover, nonsubtype-selective, state-dependent block may afford the greatest efficacy, since individual knockout of

Nav1. Based on this rationale, a decision was made to initially pursue nonsubtype selective, state-dependent Nav1 inhibitors, while monitoring molecular selectivity by testing compounds of interest on Nav1. Subsequent addition of sodium resulted in membrane depolarization and Nav1 block was quantified as interference with that cellular depolarization process. Although the initial screen on Nav1. BPBTS was found to inhibit all Nav1 subtypes with similar potency, and inhibition was dependent on membrane potential and stimulation frequency. This inhibitory mechanism was consistent with higher affinity of the compound for channels in the open and inactivated state, compared with channels in the resting state. In addition, BPBTS was two orders of magnitude more potent than the clinically used anticonvulsant and antiarrhythmic Nav1 blockers, inhibiting the inactivated state of Nav1. As such, BPBTS was an attractive lead for medicinal chemistry; its main liabilities being a poor pharmacokinetic profile. Over the course of profiling analogues of BPBTS, as well as published Nav1 inhibitors, using the membrane potentialâ€”based fluorescent screening assay, structure-based discrepancies between potencies determined in the fluorescent assay and by electrophysiology were noted for a few compounds. These discrepancies were traced to an interaction between these compounds and the agonist veratridine used to open Nav1. Subsequently, the fluorescent assay was modified such that Nav1 channels were preincubated with test compound in physiological extracellular sodium concentrations and Nav1-dependent depolarization was initiated by agonist addition Fig. Channel inhibitory potencies measured in this modified assay correlated very well with the inactivated state inhibition determined by electrophysiology across many structural classes of Nav1 inhibitors Felix et al.

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2: Wiley: Methods & Principles in Medicinal Chemistry - Editors

The most challenging aspect of ion channel drug discovery may be the identification of an appropriate, small molecule drug lead with desirable chemical properties that qualify it for exploration by medicinal chemistry (MacCoss and Baillie,). This is a key element in successful ion channel preclinical drug development.

Lagrutta and Joseph J. Ion channels are ubiquitously distributed throughout cellular life; they represent integral membrane proteins that both produce and transduce the electrical signals crucial to the maintenance and function of cells. Ion channels gate or regulate the ion flow between the cytoplasmic compartment and the extracellular space and between subcellular compartments. They open and close in response to changes in membrane potential, changes in ion concentrations on either side of the membrane, and agonist binding to the channel or closely associated regulatory proteins. Under pathological conditions ion channels contribute to or drive a variety of disease processes from achalasia and arrhythmias to xerostomia and vertigo. Ion channels can be classified in several distinct ways. The most common classification refers to the ions for which they are selective. Their primary mode of stimulus allows a classification into ligand- and voltage-gated channels. Alternatively, they can be classified by their electrophysiological properties and by their pharmacological sensitivity to toxins and synthetic drugs. Increasingly, they are classified according to their sequences, demonstrating that ion channels exist as super-families with considerable structural homology between the members, despite very different electrophysiological and pharmacological properties. Whereas our initial understanding of ion channel structure and function was largely due to electrophysiological data, our knowledge was remarkably advanced by the work of Roderick MacKinnon and his coworkers on the three-dimensional structures of potassium channels. We are now at a stage where it becomes increasingly possible to start the integration of structural and functional data to provide a detailed understanding of both channel function and how drugs interact with and modulate such channel function. A main characteristic of ion channels is their remarkable sensitivity to chemical modulation. Ion channels are excellent targets for drug design because: KGaA, Weinheim ISBN XI XII Preface channel type and subtype typically has a multiplicity of discrete ligand binding sites that are allosterically coupled to the gating and permeation machinery of the channel; and e the binding characteristics of the ligand can be modulated, both quantitatively and qualitatively, by factors such as membrane potential or channel phosphorylation. The present volume comprises eight sections, the first four of which deal with basic background information. Clinton Doering and Gerald Zamponi give a general overview on calcium channels, whereas the most important calcium channel subtypes including T-type channels by Thomas Connolly and James Barrow , L-type channels by David J. Triggle as well as N-type channels by Terry Snutch are separately treated in follow-up chapters. Then five different potassium channel subtypes and their relevant modulators are described in adequate detail. Introductory remarks to this important aspect of ion channel research are given by Dennis Wray. The concluding chapter of this volume, written by Armando Lagrutta and Joseph Salata, treats relevant safety issues in ion channel drug development. The series editors believe that this book is unique in its topic and presentation and adds a fascinating facet to the series. We are indebted to all authors for their well-elaborated contributions and we would like to thank the volume editors David Triggle, Murali Gopalakrishnan, David Rampe, and Wei Zheng for their enthusiasm to organize this volume. They are ubiquitously distributed throughout cellular life and indeed some form of ion moving and other solute moving device must have developed very early in cellular evolution and certainly must have evolved simultaneously with the development of the cell membrane. Ion channels are also one of the mechanisms by which cells respond to informational inputs. Under physiological conditions these channels permit an orderly movement of ions across cell membranes and contribute both to cellular signaling processes and to the maintenance of cellular homeostasis. Under pathological conditions ion channels contribute to or drive various diseases processes from achalasia and arrhythmias to xerostomia and vertigo. Ion channels are allosteric proteins that undergo significant conformational transitions in response to various informational

inputs, including mechanical tension, voltage gradients and endogenous and exogenous chemical signals. The latter inputs are of particular interest to the clinician, pharmacologist and the pharmaceutical industry since they represent opportunities, both real and potential, for drug intervention. However, as usual, Nature, the supreme medicinal chemist, long ago seized this opportunity and a remarkable number of toxins from venomous species are directed against both ligand- and voltage-gated ion channels. Indeed, one of the principal characteristics of ion channels is their remarkable sensitivity to chemical modulation. The chemical species depicted in Fig. Currently, there exists ion channel therapeutics for anesthesia, anxiety, epilepsy, hypertension, insomnia and pain and excellent opportunities for ion channel therapeutic modulation in, for example, affective disorders, allergic disorders, autoimmune diseases, contraception, incontinence, and stroke. Ion channels are excellent targets for drug design because they are: Loci for integrated cellular communication: Highly efficient molecular machines that permeate ions selectively at rates that can approach diffusion-controlled. There exists a multiplicity of channel types and subtypes. Each channel type and subtype typically has a multiplicity of discrete ligand binding sites that are coupled allosterically to the gating and permeation machinery of the channel. The binding characteristics of the ligand can be modulated, both quantitatively and qualitatively, by factors such as membrane potential or channel phosphorylation. There are thus provided opportunities for multiple modes of interaction that can in principle generate a common pharmacological and therapeutic endpoint. Until very recently our understanding of ion channel structure and function has been derived largely from electrophysiological data, leading to the representation depicted in Fig. Despite the cartoon-like characteristics of Fig. The past decade has seen major advances in our knowledge of channel structure and function, starting with the remarkable work of Roderick Mackinnon and his colleagues and their success in providing solid-state structures of the potassium channels. We are now at a stage where it becomes increasingly possible to start the integration of structural and functional data to provide for a detailed understanding of both channel function and of how drugs interact with and modulate such channel function. It is thus believed that this book will appear at an appropriate time in our understanding of ion channels. All four editors have worked extensively for several years on the medicinal chemistry and pharmacology of ion channels and recognize that for a successful approach to the development of new drugs active at ion channels it is increasingly necessary to follow an integrated approach. A medicinal chemistry approach in the absence of an understanding of ion channel function and behavior and without recognizing what assay technologies are telling us is not likely to be successful. Far greater integration of chemical, biochemical, biophysical, pharmacological and structural approaches are necessary. Additionally, there are drug discovery programs where it is necessary that certain types of channel-modulating behavior not be found, notably activity at HERG channels. Thus, even non-ion channel programs need to be aware of at least some aspects of ion channel structure and function. This book is organized to optimize such an interdisciplinary approach. Although the primary emphasis is on drugs active at voltage-gated calcium, potassium and sodium channels the chemical pharmacology of these drugs is set against a background of channel classification, function and structure. Accordingly, the initial chapters deal with, respectively, channel structure and function, state-dependent interactions of drugs with channels and the assay technologies for drug screening. These three initial chapters provide the necessary background for the more detailed understanding of drug actions at calcium, potassium and sodium channels. These channels are discussed in three separate sections, each of which starts with an overview of the respective channel class. The challenge will be to link that structural knowledge to the definition of channel function and to our knowledge of drug action at those channels. That should lead to therapeutic advances for arrhythmias, neurodegenerative disorders, pain and stroke, all of which are unmet or underserved medical needs and where ion channels are significant contributors to the underlying pathologies. We thank all of our contributors to this volume. They have all put aside other activities to contribute their specific knowledge and expertise and the success of the book will be entirely due to them. In excitable cells, electrical signals also have an important influence on intracellular metabolism and signal transduction, gene expression, protein synthesis and targeting, and protein degradation. In all of these

contexts, electrical signals are conducted by members of the ion channel protein superfamily, a set of more than structurally related pore-forming proteins. In addition, members of this protein superfamily are crucial in maintaining ion homeostasis in the kidney and in many different cell types and participate in calcium signaling pathways in nonexcitable cells. This introductory chapter describes the voltage-gated ion channel families and gives an overview of the common features of their structure and function. These channels are responsible for the rapid influx of sodium ions that underlies the rising phase of the action potential in nerve, muscle, and endocrine cells. Neurotoxin labeling, purification and functional reconstitution showed that sodium channels from mammalian brain contain voltage-sensing and pore-forming elements in a single protein complex of one principal a subunit of to kDa and one or two auxiliary b subunits of approximately 33 to 36 kDa Catterall, ; Catterall, a. The a subunits of sodium channels contain four homologous domains that each contain six hydrophobic, probable transmembrane segments Fig. The different members of the ion channel protein family structurally related to the voltage-gated ion channels are illustrated as transmembrane folding diagrams in which cylinders represent probable transmembrane alpha helices. Auxiliary subunits of Nav , Cav , and Kv channels are illustrated, with cylinders representing predicted alpha helices of the transmembrane subunits. N-linked carbohydrate chains are indicated by C. Intracellular auxiliary subunits are illustrated by their predicted three-dimensional structures. The pore is formed in the center of a pseudosymmetric array of the four domains, and a single a subunit containing four domains is able to receive voltage signals and activate its intrinsic pore. The channel responds to voltage by virtue of its S4 segments Fig. Drugs that block the pore of sodium channels are important as local anesthetics, antiarrhythmic drugs, and antiepileptic drugs. Nine voltage-gated sodium channel a subunits, designated Nav1. One additional related a subunit, which defines a second subfamily, Nav2. Sodium channel auxiliary subunits, Navb1 to Navb4, interact with the different a subunits and alter their physiological properties and subcellular localization. These proteins have a single transmembrane segment, a large N-terminal extracellular domain that is homologous in structure to a variable chain V-type immunoglobulin-like fold, and a short C-terminal intracellular segment Fig. The Navb subunits interact with a subunits through their extracellular Ig-fold domains, modulate a subunit function, and enhance their cell surface expression McCormick et al. Like other proteins with an extracellular Ig-fold, they also serve as cell adhesion molecules by interacting with extracellular matrix proteins, cell adhesion molecules, and cytoskeletal linker proteins Ratcliffe et al. A mutation in a conserved cysteine in the Ig-fold of the Navb1 subunit causes familial epilepsy Wallace et al. The Navb subunits are a recent evolutionary addition to the family of ion channel associated proteins, as they have only been identified in vertebrates. Skeletal muscle calcium channels, first identified by drug labeling, purification, and functional reconstitution, have a principal a1 subunit of to kDa, which is similar to the sodium channel a subunit Curtis and Catterall, ; Takahashi et al. The a1 subunit is associated with auxiliary a2d, b, and g subunits that are unrelated to the sodium channel auxiliary subunits Fig. As for the sodium channel a subunit, the calcium channel a1 subunit is sufficient to form a voltage-gated calcium-selective pore by itself. Ten functional calcium channel a1 subunits are known in vertebrates, and they fall into three subfamilies that differ in function and regulation Ertel et al. The Cav1 subfamily Cav1. L-type calcium currents also are important regulators of gene expression and other intracellular processes. The Cav2 subfamily of calcium channels Cav2. The Cav3 subfamily of calcium channels Cav3. The functional and regulatory properties and proteinâ€”protein interactions of different subfamilies of ion channels these channels are adapted to their different roles in electrical signaling and cellular signal transduction. The Cava2 and Cavd subunits are encoded by the same gene Ellis et al. Four Cava2d genes are known Arikkath and Campbell, The four Cavb subunits are all intracellular proteins with a common pattern of alpha helical and unstructured segments Ruth et al. They have important regulatory effects on cell surface expression and they also modulate the gating of calcium channels, causing enhanced activation upon depolarization and altered rate and voltage dependence of inactivation Arikkath and Campbell, Recent structural modeling and X-ray crystallography studies have revealed that these subunits contain conserved, interacting SH3 and guanylate kinase domains like the MAGUK family of scaffolding proteins Van Petegem

et al. Eight Cavg subunit genes encode glycoproteins with four transmembrane segments Jay et al. Although the Cavg1 subunit is associated specifically with skeletal muscle Cav1. Thus, the g subunits discovered as components of calcium channels apparently have a more widespread role in assembly and cell surface expression of other membrane signaling proteins. In this way, potassium channels control electrical signaling and regulate ion flux and calcium transients in nonexcitable cells.

VOLTAGE-GATED ION CHANNELS AS DRUG TARGETS (METHODS AND PRINCIPLES IN MEDICINAL CHEMISTRY) pdf

3: CiteSeerX â€” PERSPECTIVE Ion Channels as Drug Targets: The Next GPCRs

After an introduction to the topic, the authors evaluate the structure and function of ion channels, as well as related drug interaction. A section on assay technologies is followed by a section each on calcium, sodium and potassium channels.

Voltage- and ligand-gated ion channels particularly, TRP and Kv channels ; ion channel modulators; endocannabinoids; metabolomics applied to molecular pharmacology; molecular basis of the activity of natural products particularly, food-derived products ; nutraceuticals, medicinal chemistry Co-Guest Editor Prof. High-throughput screening; discovery and development of anti-nociceptive drugs; structureâ€"function studies on TRP ion channels; translational research in the field of sensory neurobiology; role of thermoTRP channels in the pathophysiology of migraine Co-Guest Editor Assist. Drug design and synthesis; pharmacokinetics; food-derived bioactive molecules; voltage-gated potassium channels; TRPM8 Special Issue Information Dear colleagues, The signal deriving from ion flux through membranes is responsible for a plethora of pivotal biological events, including hormone secretion, muscle contraction, sensation, brain information processing, and peripheral tissue control. In excitable cells, electrical signals also influence metabolism, signal transduction, gene expression, and protein synthesis, degradation, and targeting. These electrical signals are conducted by different members of the ion channel protein superfamily, composed of more than structurally related pore-forming proteins. This is the reason why voltage-gated ion channels represent an intriguing pharmacological target for the treatment of different pathologies, including pain, cardiovascular diseases, neurological and neurodegenerative disorders, cancer, and metabolic syndromes, as widely reported in the literature. In addition, channellophaties, resulting from a congenital or acquired mutation of voltage-gated ion channels, are responsible for specific and, usually, rare diseases, such as episodic ataxia, epilepsy, hyperkalemic or hypokalemic periodic paralysis, Lambertâ€"Eaton myasthenic syndrome, paramyotonia, Dravet syndrome, pain syndromes, and many others. Many efforts have been made in the last decade for the elucidation of the crystal structure of voltage-gated ion channels, their gating mechanisms, the molecular basis of their function or misfunction, their phatophysiological role, and their modulators. These are the main topics of interest of the present Special Issue that is aimed to highlight the latest advancements in this field, with a specific focus on transient receptor potential channels TRP. Original research and review articles concerning this specific matter are invited. Asia Fernandez Carvajal Assist. Once you are registered, click here to go to the submission form. Manuscripts can be submitted until the deadline. All papers will be peer-reviewed. Accepted papers will be published continuously in the journal as soon as accepted and will be listed together on the special issue website. Research articles, review articles as well as short communications are invited. For planned papers, a title and short abstract about words can be sent to the Editorial Office for announcement on this website. Submitted manuscripts should not have been published previously, nor be under consideration for publication elsewhere except conference proceedings papers. All manuscripts are thoroughly refereed through a single-blind peer-review process. A guide for authors and other relevant information for submission of manuscripts is available on the Instructions for Authors page.

VOLTAGE-GATED ION CHANNELS AS DRUG TARGETS (METHODS AND PRINCIPLES IN MEDICINAL CHEMISTRY) pdf

4: Essentials of Medicinal Chemistry and Pharmacology-Course Catalog-ACS ProEd

Encuentra Voltage-Gated Ion Channels as Drug Targets: 29 (Methods and Principles in Medicinal Chemistry) de David J. Triggle, Murali Gopalakrishnan, David Rampe, Wei Zheng, Raimund Mannhold, Hugo Kubinyi, Gerd Folkers (ISBN:) en Amazon.

Basic features[edit] Selectivity filter allowing only potassium ions through the potassium channel PBD: There are two distinctive features of ion channels that differentiate them from other types of ion transporter proteins: Ions pass through channels down their electrochemical gradient , which is a function of ion concentration and membrane potential, "downhill", without the input or help of metabolic energy e. ATP , co-transport mechanisms, or active transport mechanisms. Ion channels are located within the membrane of all excitable cells, [1] and of many intracellular organelles. This characteristic is called selective permeability. The archetypal channel pore is just one or two atoms wide at its narrowest point and is selective for specific species of ion, such as sodium or potassium. However, some channels may be permeable to the passage of more than one type of ion, typically sharing a common charge: Ions often move through the segments of the channel pore in single file nearly as quickly as the ions move through free solution. In many ion channels, passage through the pore is governed by a "gate", which may be opened or closed in response to chemical or electrical signals, temperature, or mechanical force. Ion channels are integral membrane proteins , typically formed as assemblies of several individual proteins. Such "multi- subunit " assemblies usually involve a circular arrangement of identical or homologous proteins closely packed around a water-filled pore through the plane of the membrane or lipid bilayer. Biological role[edit] Because channels underlie the nerve impulse and because "transmitter-activated" channels mediate conduction across the synapses , channels are especially prominent components of the nervous system. Indeed, numerous toxins that organisms have evolved for shutting down the nervous systems of predators and prey e. In addition, ion channels are key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac , skeletal , and smooth muscle contraction , epithelial transport of nutrients and ions, T-cell activation and pancreatic beta-cell insulin release. In the search for new drugs, ion channels are a frequent target. Further heterogeneity of ion channels arises when channels with different constitutive subunits give rise to a specific kind of current. Classification by gating[edit] Ion channels may be classified by gating, i. Voltage-gated ion channels open or close depending on the voltage gradient across the plasma membrane, while ligand-gated ion channels open or close depending on binding of ligands to the channel. Voltage-gated ion channel Voltage-gated ion channels open and close in response to membrane potential. This family contains at least 9 members and is largely responsible for action potential creation and propagation. These channels play an important role in both linking muscle excitation with contraction as well as neuronal excitation with transmitter release. Cation channels of sperm: This small family of channels, normally referred to as Catsper channels, is related to the two-pore channels and distantly related to TRP channels. Voltage-gated potassium channels KV: This family contains almost 40 members, which are further divided into 12 subfamilies. These channels are known mainly for their role in repolarizing the cell membrane following action potentials. Correspondingly, they assemble as tetramers to produce a functioning channel. Some transient receptor potential channels: This group of channels, normally referred to simply as TRP channels, is named after their role in Drosophila phototransduction. This family, containing at least 28 members, is incredibly diverse in its method of activation. This family is subdivided into 6 subfamilies based on homology: Hyperpolarization-activated cyclic nucleotide-gated channels: The opening of these channels is due to hyperpolarization rather than the depolarization required for other cyclic nucleotide-gated channels. As these channels open under hyperpolarizing conditions, they function as pacemaking channels in the heart, particularly the SA node. Voltage-gated proton channels open with depolarization, but in a strongly pH-sensitive manner. The result is that these channels open only when the electrochemical gradient is outward, such that their opening will only

allow protons to leave cells. Their function thus appears to be acid extrusion from cells. Another important function occurs in phagocytes e. NADPH oxidase is electrogenic, moving electrons across the membrane, and proton channels open to allow proton flux to balance the electron movement electrically. Ligand-gated ion channel Also known as ionotropic receptors , this group of channels open in response to specific ligand molecules binding to the extracellular domain of the receptor protein. Ligand binding causes a conformational change in the structure of the channel protein that ultimately leads to the opening of the channel gate and subsequent ion flux across the plasma membrane. Ion channels activated by second messengers may also be categorized in this group, although ligands and second messengers are otherwise distinguished from each other. Other gating[edit] Gating also includes activation and inactivation by second messengers from the inside of the cell membrane â€" rather than from outside the cell, as in the case for ligands. These channels allow potassium ions to flow into the cell in an "inwardly rectifying" manner: This family is composed of 15 official and 1 unofficial members and is further subdivided into 7 subfamilies based on homology. They are involved in important physiological processes such as pacemaker activity in the heart, insulin release, and potassium uptake in glial cells. They contain only two transmembrane segments, corresponding to the core pore-forming segments of the KV and KCa channels. Light-gated channels like channelrhodopsin are directly opened by photons. Mechanosensitive ion channels open under the influence of stretch, pressure, shear, and displacement. This superfamily of channels contains two families: This grouping is functional rather than evolutionary. There are 6 members of this family, which is divided into 2 subfamilies. Classification by type of ions[edit] Chloride channels: This superfamily of channels consists of approximately 13 members. These channels are non-selective for small anions; however chloride is the most abundant anion, and hence they are known as chloride channels.

5: Voltage-Gated Ion Channels as Drug Targets - PDF Free Download

Voltage-Gated Ion Channels as Drug Targets. Methods and Principles in Medicinal Chemistry (Bd. 31). Herausgegeben von David J. Triggle, Murali Gopalakrishnan, David Rampe und Wei Zheng.

6: Ion channel - Wikipedia

Edited by the most prominent person in the field and top researchers at US pharmaceutical companies, this is a unique resource for drug developers and physiologists seeking a molecular-level understanding of ion channel pharmacology.

7: Ion Channels as Drug Targets: The Next GPCRs

Preface The present volume of our series "Methods and Principles in Medicinal Chemistry" is dedicated to "Voltage-gated Ion Channels" and their impact as targets for drug design. Ion channels are ubiquitously distributed throughout cellular life; they represent integral membrane proteins that both produce and transduce the electrical.

VOLTAGE-GATED ION CHANNELS AS DRUG TARGETS (METHODS AND PRINCIPLES IN MEDICINAL CHEMISTRY) pdf

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