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Minireview

Targeting the α2-δ calcium channel subunit for pain therapeutics

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CONTENTS

Abstract

Voltage-gated calcium channels (VGCCs) play an important role in the transmission of nociceptive information. Previous studies have focused on targeting the α1 subunit of VGCCs, specifically the N-type and T-type VGCCs, for the development of analgesic drugs. New research has highlighted an underlying role for the auxiliary α2-δ subunit in *in vivo* models of neuropathic pain. Further evidence that the marketed pain therapies gabapentin and pregabalin target α2-δ subunits within the VGCC to pharmacologically modulate calcium channel signaling and attenuate nociceptive transmission, thus alleviating pain symptoms, has prompted the development of novel α2-δ ligands as candidate analgesics. This article will highlight promising novel compounds emerging in the recent literature.

Introduction

Voltage-gated calcium channels (VGCCs) mediate calcium influx in response to membrane depolarization and regulate intracellular processes such as contraction, secretion, neurotransmission and gene expression in many different cell types. VGCCs are made up of four or five distinct subunits (1), as depicted in Figure 1. The largest is the α1 subunit, formed by four homologous domains (I-IV), each of which comprises six transmembrane segments (S1-S6) to make up the conduction pore, the voltage sensor and gating apparatus. An intracellular β subunit and a transmembrane, disulfide-linked α2-δ subunit complex are components of most types of calcium channels. γ Subunits are found in skeletal muscle calcium channels, and related subunits are expressed in heart and brain (2).

Neurotransmission via VGCCs plays an important role in nociceptive responses and previous studies have focused on the pharmacological and electrophysiological role of α1 subunits, which have been divided into numerous subtypes (see Table I) and differ in tissue location and peptide specificity. L-, N-, P/Q-, R- and T-type VGCCs abound in the nerve terminus and are classified according to their sensitivity to toxins. N-type and T-type calcium channels have emerged as attractive targets for the development of new analgesic drugs (3, 4).

Auxiliary subunits support the membrane trafficking of the α1 subunit and modulate the kinetic properties of the channel. In particular, the α2-δ subunit has been shown to modify the biophysical and pharmacological properties of the α1 subunit (5). Molecular diversity within the α2δ subunit has been described, with the identification of four subunit genes to date: α2-δ1, α2-δ2, α2-δ3 (6) and α2-δ4 (7). Recent studies have demonstrated a role for the auxiliary α2-δ1 subunit in the processing of painful sensory information and, therefore, this review will highlight new products that target α2-δ subunits to modulate calcium channel functions. These emerging compounds represent promising candidates for further study as pain therapeutics.

Therapeutic targeting of the α2-δ calcium channel subunit

In vivo studies have demonstrated increased α2-δ1 expression in dorsal root ganglion (DRG) and spinal dorsal horn neurons following peripheral nerve injury, correlating with the onset of neuropathic pain symptoms (8, 9). Furthermore, transgenic mice overexpressing the α2-δ1 subunit exhibit hypersensitivity to mechanical and thermal stimuli and prolonged post-stimulation neuronal firing in the dorsal horn of the spinal cord (10).

As described above, α2-δ1 is emerging as a promising analgesic target for painful syndromes. Gabapentin (Neurontin®) and pregabalin (Lyrica™), GABA analogues that have both been launched by Pfizer for the treatment of neuropathic pain syndromes and postherpetic neuralgia, have been postulated to interact with this novel calcium channel binding site to diminish axonal membrane excitability, without completely blocking channel function (11). Gabapentin is also under phase III clinical investigation as a therapy for pain associated with carpal tunnel

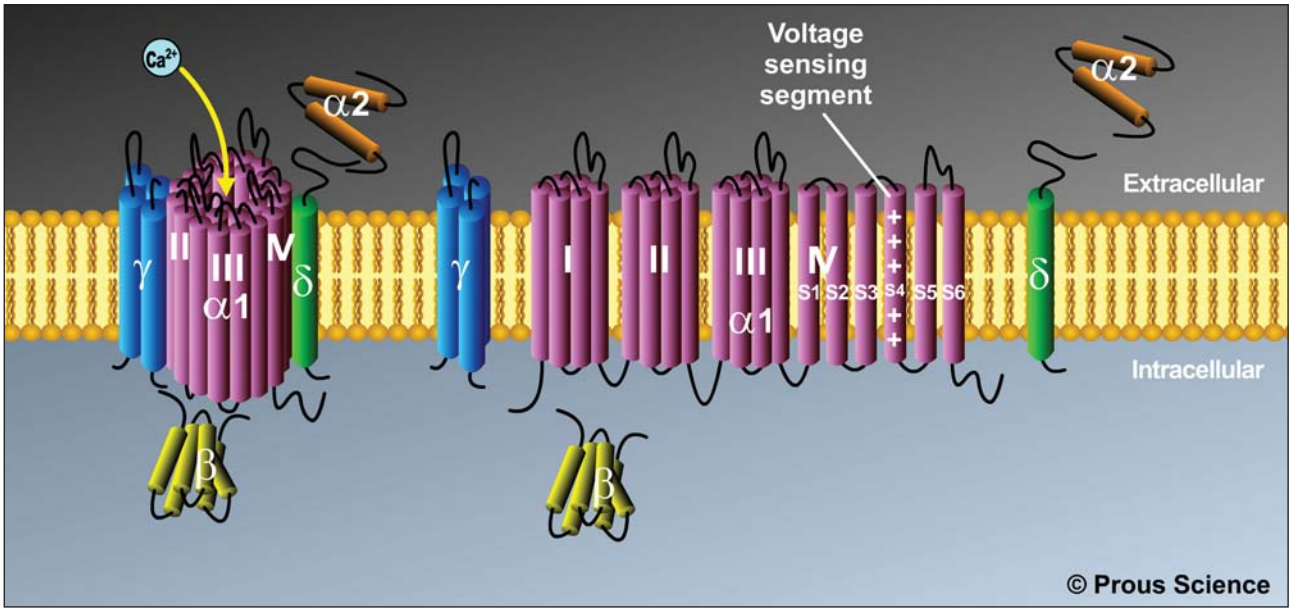


Fig. 1. The subunits of a voltage-gated calcium channel.

Table I: α1 Subunits and their voltage classification.

Subtype	Classification
α1A ($Ca_V2.1$)	P/Q-type
α1B ($Ca_V2.2$)	N-type
α1C ($Ca_V1.2$)	L-type
α1D ($Ca_V1.3$)	L-type
α1E ($Ca_V2.3$)	R-type
α1F ($Ca_V1.4$)	?
α1G ($Ca_V3.1$)	T-type
α1H ($Ca_V3.2$)	T-type
α1I ($Ca_V3.3$)	T-type
α1J ($Ca_V1.1$)	L-type

syndrome (12), with further clinical studies assessing its efficacy in improving postoperative pain in surgical patients (13). Pregabalin is also progressing in phase III clinical studies for fibromyalgia (14, 15). Several novel, specific α2-δ subunit ligands are emerging in the literature as potential analgesics (see Table II).

Drug discovery lines are also focusing on the development of gabapentin prodrugs (see Table III). Although gabapentin is effective orally, its pharmacokinetic profile is thought to be improvable as, following oral absorption, rapid clearance necessitates drug administration 3-4 times a day in order to maintain therapeutic levels. In addition, saturation of the intestinal transporter responsible for gabapentin absorption has led to unpredictable drug exposure and potentially ineffective therapy in certain patients.

Xenoport has developed XP-13512 (gabapentin enacarbil), a novel prodrug of gabapentin designed for absorption throughout the intestine by high-capacity nutrient transporters. Administration of XP-13512 has been shown to improve gabapentin bioavailability, dose-proportionality and colonic absorption in animal and human

Table II: Selected α2-δ subunit ligands reported in current literature and patents.

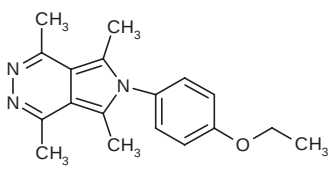
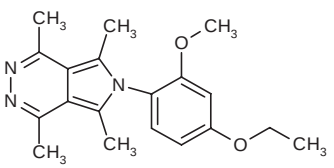
Source	Integrity EN	Structure	Refs.
Merck & Co.	364844		20, 21
	372697		

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Table II (Cont.): Selected $\alpha 2$-δ subunit ligands reported in current literature and patents.

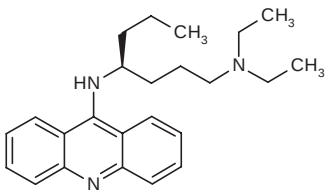
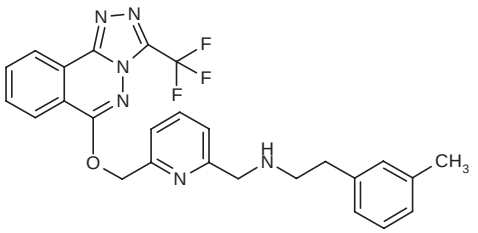
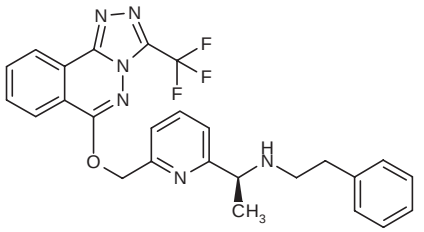
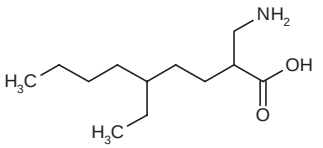
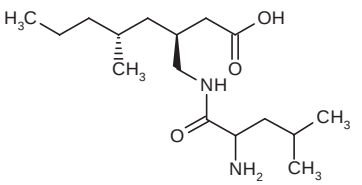
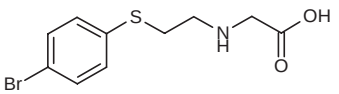
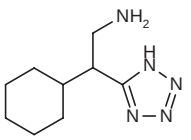
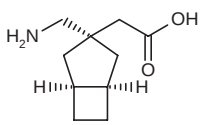
Source	Integrity EN	Structure	Refs.
Merck & Co.	367807		22, 23
	373503		24, 25
	373505		
Pfizer	402509		26, 27
	402512		28
	364990		29
	382213		30
	304123		32

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Table II (Cont.): Selected α2-δ subunit ligands reported in current literature and patents.

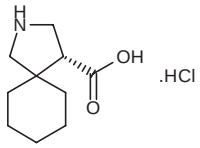
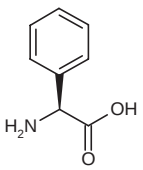
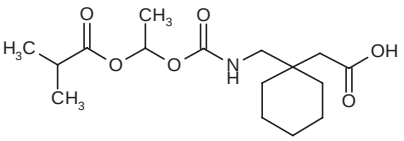
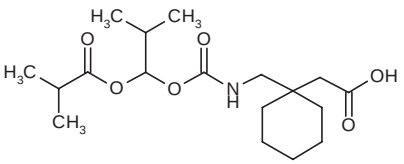
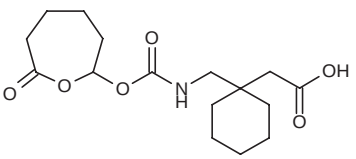
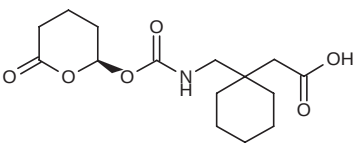
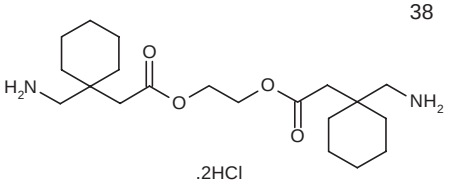
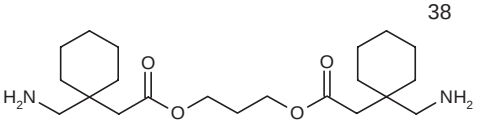
Source	Integrity EN	Structure	Refs.
Pfizer	280081		32
Abbott	417780		33, 34

Table III: Emerging prodrugs of gabapentin.

Source	Integrity EN	Drug Name/Chemical Name	Structure	Refs.
Xenoport Astellas Pharma	332087	Gabapentin enacarbil		16, 17 19, 35
Xenoport	332088	2-[1-[1-(Isobutyryloxy)-2-methyl-propoxycarbonylaminomethyl]cyclohexyl] acetic acid		36
	350699	2-[1-(7-Oxooxepan-2-yloxycarbonyl aminomethyl)cyclohexyl]acetic acid		37
	350701	2-[1-[6-Oxotetrahydropyran-2(*R*)-yloxycarbonylaminomethyl]cyclohexyl] acetic acid		37
Academy of Military Sciences	373539	Bis[2-[1-(aminomethyl) cyclohexyl]acetic acid]ethane-1,2-diyl diester dihydrochloride	 .2HCl	38
	373542	Bis[2-[1-(aminomethyl) cyclohexyl]acetic acid]propane-1,3-diyl diester dihydrochloride	 .2HCl	38

pharmacokinetic studies (16-18). Recent data from a multicenter, double-blind phase II clinical trial have shown that XP-13512 is effective in the treatment of postherpetic neuralgia (PHN), reducing both pain scores and sleep interference (18). Astellas Pharma has in-licensed XP-13512 from XenoPort and is conducting phase I trials in Japan for neuropathic pain (19).

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