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S1PR2 and S1PR3 as Emerging Targets for Treatment of Chronic Pain

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Abstract: Chronic pain has posed a serious challenge for many people's daily life all over the world, with approximately 41% of Europeans in developing countries suffering it. Until recently, major treatments have relied on agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and narcotics, which, however, have become less acceptable due to side-effects. Therefore, novel classes of pain-relievers are urgently needed to fill this void and improve the life quality of patients.

Sphingosine-1-phosphate (S1P) is one of the most notable lysophospholipids, whose role on pain generation has been increasingly recognized. Drugs targeting sphingosine-1-phosphate receptors (S1PRs) could be developed as novel analgesics, either as monotherapy or potential adjuncts. In this review, recent advances of the roles of S1PRs in peripheral sensory aspects are summarized, especially S1PR3 and S1PR2.

Keywords: S1P, S1PRs, Chronic pain, Rheumatoid arthritis

1. METABOLIC PATHWAY AND FUNCTION OF S1P

S1P is generated by phosphorylation of sphingosine in reactions catalyzed by sphingosine kinase 1&2 (SPHK 1&2)[1] in cells like immune cells, epithelial cells and neurons when stimulated by chemo-attractants such as tumour necrosis factor (TNFα) and nerve growth factor (NGF)[2, 3]. Both extracellular and intracellular level of S1P are tightly regulated to ensure a low constitutive level of S1P in most tissues[3], but high concentrations of free S1P would occur at inflammation sites with releasing of activated immune-competent cells[2].

S1P has received much attention owing to its potential role in diverse cellular processes in inflammation and immune responses like cell survival, proliferation, differentiation, migration, adhesion, lymphocyte trafficking, cytokine and chemokine production[3], etc.

Recent findings have also identified important roles of S1P for modulating sensory neuronal excitability[2, 4, 5], which has been implicated in pain and pain hypersensitivity[5, 6]. Additional studies demonstrated that S1P augmented both heat- and capsaicin-activated membrane currents in all size classes[7] of mouse sensory neurons. Furthermore, according to recent reports, S1P mediates both antinociception and pronociceptive effects in central nerve system (CNS) and peripheral nerve system (PNS), respectively[8]. Thermal antinociception was produced after the intracerebroventricular administration of S1P in mice[9], suggesting that the antinociceptive role of S1P in CNS. In contrast, increased nociceptive sensitivity arose after the administration of S1P in DRG[7], indicating the pronociceptive role of S1P in PNS. Although the role of S1P in CNS and PNS is different, not all studies have noticed this and still used DRG to study the block of pain from original but concluded without emphasis of this important distinction. Therefore, more attention should be paid about the distinction during the description of the conclusion in future.

Taken together, the concept that S1P not only regulates inflammation but simultaneously contributes to pain sensitivity is interest. If so, the development of agonists or antagonists targeting S1P-S1PR signals would be of great

clinical benefit for chronic pain in many diseases like RA.

2. S1PRs

S1P functions most through S1PR 1-5, a family of five G protein-coupled receptors originally named Edg receptors. Several reports supported the expression of S1PR 1-3 in DRG neurons[2, 10], whereas the expression of S1PR 4&5 was controversially discussed[2, 10] with only a few researches supporting the expression of S1PR4[4, 10] or S1PR5[11]. The research-based on S1PR1 has been done extensively, therefore the focus of this review will be on S1PR 2&3 as well as their modulators.

Table 1. Existing agonists and antagonists of S1PR2&3[8, 12]

	Agonists	Antagonists
S1PR2	CYM-5520, CYM5478, XAX-126	JTE-013
S1PR3	VPC23153, FTY720-P	CAY10444, VPC01091, VPC-23019

2.1. THE ROLE OF S1PR3

With the extensive research and application of S1PR1 in the sensory field, the role of S1PR3 in sensory neurons has been focused recently due to a series of notable phenomena. After exposing to S1P, a slowly activating and deactivating inward current was also observed in many neurons, followed by S1PR1-mediated pro-algesic action[5]. In addition, some sensory neurons treated with S1PR1-targeted siRNA were still capable of increasing excitability under treatment of S1P. These all far support the idea that there must be other S1PRs capable of mediating the S1P-induced enhancement of excitability, not only S1PR1[10]. The same scholar who discovered this problem later confirmed this idea and supplemented the conclusion as “the enhanced excitability produced by S1P is mediated by activation of S1PR1 and/or S1PR3”, which has since been confirmed by a growing number of scholars[5, 6] in different perspectives. For example, Hill RZ et al. exemplified in studies using blocking technique and antagonist treatment, showed that loss of S1PR3 decreases mechanical sensitivity and inflammatory pain, together with a selective S1PR3 antagonist can decrease action potential (AP) firing and inflammatory hypersensitivity[6].

2.2. APPLICATION OF S1PR3 MODLATORS

With the increased attention of S1PR3, more and more studies on its agonists and antagonist have been conducted (Table 1.). Although there was no clinical application case, it has been often used in experiments to study the function of receptors. CYM5541 is a well-applicated selective S1PR3 agonist, one of its researches showed that low concentration could not change both AP firing and resting membrane potential (RMP), medium concentration caused dramatical AP firing change but not RMP, high concentration changed RMP obviously, at the meantime two apparent APs in depolarization and recovery period were produced[13]. This was later proved by the same author that high-concentrated CYM5541 depolarized the neuronal membrane by not only S1PR3 but also S1PR1. These observations suggested that the drug concentration is a non-negligible factor during application. In the future, antagonists targeting S1PR3 showed in Table 1. may play as important a role in pain inhibition as S1PR1, and other selective antagonists still need to be developed.

2.3. THE ROLE OF S1PR2

There are a limited number of studies specifically focused on S1PR2. There are shreds of evidence captured from parts of studies about other S1PRs showed that S1PR2 itself cannot increase neuronal excitability[13] but S1PR2 antagonist JTE-013 itself can ameliorate neuronal excitability, which indicates S1PR2 may have inhibitory function

rather than excitatory function. Indeed, few pieces of research have been undertaken to explore the sensory effect of S1PR2 in some diseases. For example, a study about neuropathic pain showed S1PR2 deficiency can reduce mechanical threshold and hence increase pain sensitivity in the mouse model[14]. Another study about chronic constriction injury (CCI) rats demonstrated that S1PR2 overexpression can raise mechanical and thermal pain thresholds while knockdown of S1PR2 aggravated pain sensitivity[15]. Intriguingly, the effect of S1PR2 on pain sensitivity can be abolished by activation of S1PR1 using its specific agonist, CYM-5442, which suggests S1PR2 owning different mechanisms with S1PR1 in terms of hyperalgesia development[15]. Future applications of S1PR2 in other disease models like RA are considered promising.

2.4. APPICATION OF S1PR2 MODULATORS

Regarding S1PR2, all evidence suggests that S1PR2 may play inhibitory roles in peripheral sensation, if so, agonist-induced activation of S1PR2 constitutes a novel therapy for the treatment of pain. However, the detailed functions of S1PR2 are still rudimentarily understood, and hence the development of selective agonists and antagonists is much behind that of S1PR 1&3 (Table 1.). Early on, JTE-013 was developed as a selective S1PR2 antagonist and used in numerous studies to unravel possible functions of S1PR2, during which both of its time- and concentration-dependent effects on excitability together with its narrow activation range was reported. However, later it was proved that JTE-013 was capable of functioning in the condition of lacking S1PR2[16] and even working on other S1PRs. Its exhibited low selectivity, together with low potency and short half-life led to the development of many derivatives with better potency, such as AB1[17]. Interestingly, a series of S1PR2 agonists have also been described like CYM5520, CYM5478 and XAX-126, but so far their biological effects are poorly understood and hence there are no in vivo reports[12]. Taking one with another, it remains to be further studied whether S1PR2 related drugs, like selective S1PR2 agonists, can also be applied to the treatment of pain in certain diseases like RA.

3. LIMITATION AND FUTURE DIRECTION

In conclusion, with the deepening of research on the function of S1PRs in the sensory area, the function of S1PR3 to accelerate hyperalgesia has gradually come into our view. Therefore, the application of S1PR3 antagonists has been discussed too. S1PR2, however, is rarely valued in contrast. What is easily overlooked is that S1PR2 may have an inhibitory effect on neuronal excitation which is opposite to that of S1PR 1&3. Therefore, using selective S1PR2 agonists instead of antagonists may explore a new idea for related analgesic research. Few studies indicated that S1PR 4&5 are not sufficient to mediate the S1P-induced sensitization, but whether they have supplementary or other function remains unknown. Overall, the family of S1PRs appears worthy of continued study and may provide significant therapeutic opportunities in many areas especially pain area[18], and new generation S1PR drugs are also needed to be developed to target more specific S1PRs. Besides all advances of S1PRs in the sensory area and relevant drug, some limitations in past researches like techniques for inhibiting a receptor, the difference between human and mouse DRG, the difference between in vivo and in vitro and drug tolerance, etc. still need to be considered.

In addition, there is evidence showed that S1P not only can directly increase the excitability of rat nociceptor sensitivity and cause thermal hyperalgesia[19] in vitro[4] and in vivo[2] but also can exert its actions at least in part via the upregulation of peroxynitrite[19]. This demonstration about the other functional pathway of S1P besides through S1PRs is also an interesting topic. Besides, previous in vitro studies of S1P on sensory neurons mainly focused on small-diameter neurons, but evidence from a study suggests that larger diameter neurons may also play important roles in mediating pain behaviours in various rodent pain models[20]. The study of neurons with different diameters is another topic of concern.

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