CNS-Penetrant LPA$_1$ Antagonist PIPE-791 Provides Superior Analgesia Compared to Peripherally-Restricted CTX-343 in a Rat Model of LPA-Induced Osteoarthritis

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Introduction

Lysophosphatidic acid (LPA) signaling through the LPA$_1$ receptor contributes to the development of chronic joint pain in osteoarthritis (OA), yet the relative contributions of peripheral versus central LPA$_1$ signaling remain poorly understood. In this study, we evaluated the efficacy of PIPE-791, a CNS-penetrant LPA$_1$ antagonist, versus CTX-343, a peripherally-restricted analog, in a weight-bearing rat model of osteoarthritis (OA) induced by intra-articular LPA injection. Rats were dosed with either PIPE-791 or CTX-343. Next, rats received unilateral intra-articular injections of LPA to induce joint inflammation and sustained pain behavior. Weight-bearing asymmetry was assessed with an incapacitance meter. PIPE-791 treatment significantly restored weight distribution to the affected limb out to 72h, while CTX-343 had a more modest effect, supporting that blocking LPA1 centrally and peripherally provides superior efficacy than peripheral alone.

In the periphery, satellite glial cells (SGC) in the dorsal root ganglion (DRG) express high levels of LPA1 a result confirmed by our research. During neuropathic pain, it has been proposed that aberrant LPA1 signaling leads to secretion of pronociceptive factors. To better understand this, we collected lumbar dorsal root ganglion (peripheral) and spinal cord (central) tissue from rats 24h after intra-articular LPA injection. In the DRG, we observed induction of glial fibrillary acidic protein (*Gfap*) transcript in lumbar DRGs, indicative of SGC activation. We also observed LPA-mediated increases in *Il-6* and *Enpp2* (autotaxin). Importantly, PIPE-791 treatment prevented induction in each of these markers. In the lumbar spinal cord, we saw PIPE-791 sensitive upregulation of *Il-6* and autotaxin. We also measured IL-6 protein in lumbar spinal cord tissue and observed an LPA-mediated increase in IL-6 protein that was reduced with PIPE-791.

These findings demonstrate that CNS penetration is a key determinant of therapeutic efficacy for LPA1 antagonism in OA pain. We hypothesize that an OA insult activates SGCs and the synthesis of pronociceptive signals (i.e., IL-6 and ATX). These, in turn, signal to upregulate production of IL-6 and LPA in the spinal cord and may help explain the superior efficacy with a CNS-penetrant antagonist. Of note, neuropathic pain can be ameliorated by CNS administration of either an anti-IL-6 antibody or an autotaxin inhibitor. As such, PIPE-791's superior analgesic profile highlights the importance of targeting central LPA1 signaling and supports further development of CNS-penetrant LPA1 antagonists for OA and neuropathic pain.

LPA1 is highly expressed in DRG and spinal cord

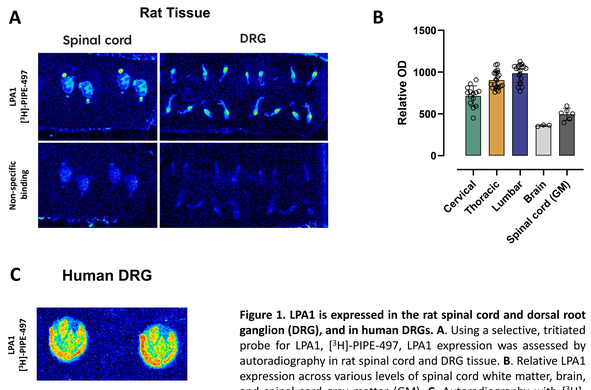

Figure 1. LPA1 is expressed in the rat spinal cord and dorsal root ganglion (DRG), and in human DRGs. A. Using a selective, tritiated probe for LPA1, [^{3}H]-PIPE-497, LPA1 expression was assessed by autoradiography in rat spinal cord and DRG tissue. **B**. Relative LPA1 expression across various levels of spinal cord white matter, brain, and spinal cord gray matter (GM), **C**. Autoradiography with [^{3}H]-PIPE-497 showing high expression of LPA1 in human DRG tissue (19 yo, male). Each dot represents a separate image.

PIPE-791, CTX-343 properties

	PIPE-791	CTX-343
24 hr LPA1 Calcium flux IC_{50} (nM)	9.9	44.1
Cl_u (mL/min/kg), $t_{1/2}$ (h), F (%)	61, 7, 78	15, 5, 105
$K_{p,uu,2h}$ (brain), $K_{p,uu,2h}$ (liver)	0.47, 6.2	0.05, 24.3
$[Brain]_{2h}$, $[Liver]_{2h}$ (µM)	5.2, 28.9	0.29, 59.8
Human hepatocyte incubation $t_{1/2}$ (mins), Cl_{int} (mL/min/kg), ER	*1153, 3.13, 0.13*	*>7600, <0.46, 0.02*
Mouse brain LPA1 Occupancy ED_{50}	0.03 mpk @ steady state	Not tested
General and Cholestatic Hepatotox	None @ 30µM	None @ 100 µM

Figure 2. Table abbreviations. Cl_u = drug clearance $t_{1/2}$ = half-life, $K_{p,uu}$ = unbound tissue to plasma ratio, F(%) oral bioavailability, Cl_{int} = *intrinsic clearance, ER = Extraction Ratio.* Values derived from rat unless otherwise noted.

LPA1 alleviates pain in a chemotherapy-induced pain model

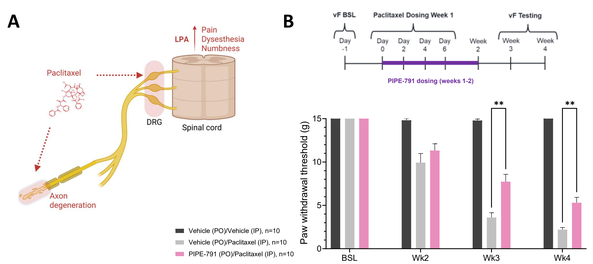

Figure 3. PIPE-791 alleviates pain in a paclitaxel-induced mechanical allodynia model A. Spinal lysophosphatidic acid (LPA) levels are elevated following paclitaxel administration, indicating activation of LPA signaling pathways (Uchida et al., 2013). B. Adult male Wistar rats treated with PIPE-791 for two weeks resulted in a partial but statistically significant reduction in mechanical allodynia as assessed by von Frey test. ** p < 0.01, n=10/group.

PIPE-791 ameliorates LPA-Induced Rat OA

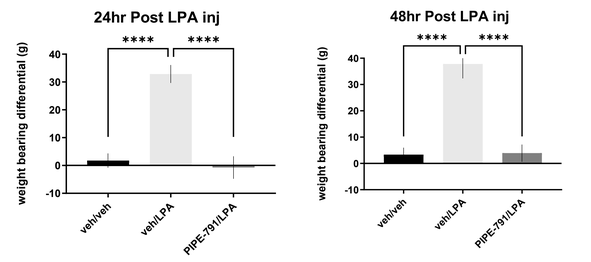

Figure 4. PIPE-791(3mg/kg) ameliorates pain in a lysophosphatidic acid (LPA)-induced osteoarthritis rat model (McDougall et al., 2017). Behavioral assessments indicate that PIPE-791 mitigates LPA-induced joint pain, as evidenced by improved weight-bearing symmetry and reduced mechanical allodynia. Data are presented as mean ± SEM; (****p < 0.001; 1-way ANOVA, Dunnett's post-hoc, n=5)($^{\$}$p < 0.05; unpaired t test).

PIPE-791 inhibits OA-induced changes in gene expression

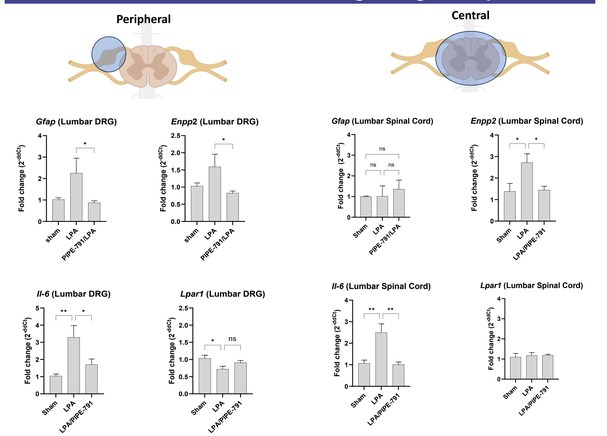

Figure 6. Osteoarthritic insult results in LPA1-sensitive increases in transcript expression in DRGs (peripheral) and spinal cord (central). A. In DRGs, *Gfap*, *Enpp2*, and *Il-6* increase in response to OA insult. Inhibited by PIPE-791 (* p < 0.05, ** P < 0.01; 1-way ANOVA, Dunnett's post-hoc, n=8). LPAR1 was unchanged. Table of additional mRNAs tested but did not reach statistical significance (n=4). B. In spinal cord, *Enpp2* and *Il-6* increase in response to OA insult. GFAP and LPAR1 are unchanged (* p < 0.05, ** P < 0.01; 1-way ANOVA, Dunnet's post-hoc, n=8). Corresponding tissue regions collected highlighted in light blue.

Methods

Figure 8, Experimental design for Figure 4. Male Lewis rats received their first dose of vehicle (PO) or PIPE-791(3mg/kg) (PO) 24 hours prior to LPA injection. Baseline weightbearing assessments were conducted 1 hour before LPA administration. A second dose of the respective treatment was administered 1 hour post-LPA injection. Weightbearing was reassessed 24 hours post-LPA, followed by a third dose of the respective treatment 1 hour after this test. Final weightbearing measurements were taken 48 hours post-LPA injection.
Experimental design for Figure 5. Male Lewis rats received their first dose of vehicle (PO), CTX-343(3mg/kg) (PO), or PIPE-791(3mg/kg) (PO) 24 hours prior to LPA injection. Baseline weightbearing assessments were conducted 1 hour before LPA administration. A second dose of the respective treatment was administered 1 hour post-LPA injection. Weightbearing was reassessed 24 hours post-LPA, followed by a third dose of the respective treatment 1 hour after this test. Final weightbearing measurements were taken 48 hours post-LPA injection.

PIPE-791 superior to CTX-343 in LPA-Induced Rat OA

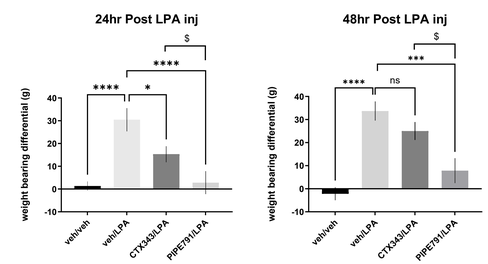

Figure 5. PIPE-791(3mg/kg) demonstrates superior efficacy over CTX-343(3mg/kg) in a lysophosphatidic acid (LPA)-induced rat model of osteoarthritis (OA). Representative data from LPA-induced OA rats treated with either PIPE-791 or CTX-343. Behavioral assessment of weight-bearing asymmetry demonstrates improved functional outcomes in the PIPE-791 group. Data are presented as mean ± SEM; (*p < 0.05, ***p < 0.01 vs. CTX-343; ****p < 0.001; 1-way ANOVA, Dunnett's post-hoc, n=5)($^{\$}$p < 0.05; unpaired t test) . ns: not-significant.

OA increases IL-6 in spinal cord (48hr) and is LPA1 sensitive

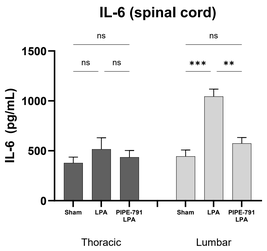

Figure 7. Osteoarthritic insult results in an LPA1-sensitive increase in IL-6 protein levels in spinal cord tissue 48 hours after insult. IL-6 induction is inhibited by pre-treatment with PIPE-791 (** p < 0.01, *** p < 0.001; 1-way ANOVA, Dunnett's post-hoc, n=4). ns: not-significant.

Conclusion

Our findings demonstrate that CNS-penetrant LPA$_1$ antagonism with PIPE-791 provides superior analgesic efficacy compared to the peripherally-restricted CTX-343 in a rat model of LPA-induced osteoarthritis. PIPE-791 not only restored weight-bearing behavior but also prevented OA induced transcriptional and protein level changes in both peripheral (DRG) and central (spinal cord) compartments. These results underscore the importance of targeting both peripheral and central LPA$_1$ signaling in chronic joint pain. These data support the continued development of CNS-penetrant LPA$_1$ antagonists for osteoarthritis and potentially other neuropathic pain conditions. Efficacy in a CIPN model suggests that antagonizing LPA1 may also be more broadly applicable to other indications, including chemotherapy-induced peripheral neuropathy.

PIPE-791 has shown efficacy in a non-human primate model of neuropathic pain (Hama et al., 2025) and is currently in a clinical trial for osteoarthritis and lower back pain (NCT06810245)

References

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