INTRODUCTION
Cannabinoid receptors have been extensively explored as targets to modulate a wide variety of pain modalities. The cannabinoid 2 (CB2) receptor has received significant attention as a target that may provide pain relief without the central nervous system (CNS) liabilities associated cannabinoid 1 (CB1) receptor modulation.1 Although selective CB2 receptor agonists have shown great promise in preclinical models, the efficacy observed in these models has not translated into the clinical setting. In detailed pharmacologic studies of selective CB2 agonists, we encountered abnormal pharmacokinetic (PK)/pharmacodynamic relationships for numerous compounds in an osteoarthritis (OA) pain animal model, whereby efficacy, safety, and tolerability were not concordant. CB2 agonists were partial agonists, particularly in promoting receptor internalization and recycling activity, a critical step in receptor recycling required for maintenance of efficacy. In rat pain models, CB2 agonists were highly efficacious in the first hour following administration but then rapidly lost efficacy despite sustained plasma exposures. In contrast, the in vivo efficacy of full agonists was maintained as long as plasma levels remained sufficient to activate receptor efficacy. These studies allowed the identification of APD371, a full agonist at human and rat CB2 receptors with >1000-fold selectivity versus the CB1 receptor. The unique pharmacologic profile provided efficacy in numerous animal pain models commensurate with the PK profile. These data support the unique receptor pharmacology of APD371, a highly efficacious, full agonist at CB2 receptor that is currently being evaluated in 2 clinical trials for visceral pain associated with Crohn’s disease.

METHODS

RESULTS

Figure 1. Acute tachyphylaxis of antinociceptive effect of a partial cannabinoid 2 (CB2) agonist in rat osteoarthritic pain model. (A) Efficacy, % of CP55,940. (B) Time to peak antinociception following administration of partial CB2 agonist with >1000-fold selectivity versus the CB1 receptor. (C) Plasma concentrations of APD371 and APD373 at trough doses following oral dosing. (D) Pharmacokinetic/pharmacodynamic relationship for APD371 in rat MIA model for OA pain. Antinociceptive efficacy of APD371 is maintained as long as plasma drug levels are maintained above 200 ng/mL by osmotic pump delivery. (E) Pharmacodynamic/pharmacokinetics relationship for compound 1 in rat osteoarthritis pain model. Antinociceptive efficacy is rapidly lost while plasma levels remain high (2430 ng/mL). Paw withdrawal threshold (PWT) is plotted along with the plasma drug levels at the indicated time points after oral drug administration, 20 mg/kg. (F) Graph showing APD371-induced antinociception in a murine model of OA pain. (G) APD371: A Potent, Highly Selective, Full Agonist of the Human CB2 Receptor With Sustained Analgesic Effects in Rodents

SUMMARY AND CONCLUSIONS
- Selective CB2 partial agonists show transient efficacy in rodent model of OA pain, despite sustained plasma exposure
- Partial agonists induce CB2 receptor desensitization in vitro, presumably because of inefficient receptor internalization and recycling, following activation
- APD371 is a highly selective full agonist at the CB2 receptor in recombinant cells and retains full efficacy at endogenous CB2 receptors in primary cells
- Upon chronic administration, APD371 maintains full efficacy in OA pain model as long as plasma drug levels are maintained
- These data support the unique profile of APD371 that is currently being evaluated in a phase 2 clinical trial for visceral pain associated with Crohn’s disease.

REFERENCES

APD371: A Potent, Highly Selective, Full Agonist of the Human CB2 Receptor With Sustained Analgesic Effects in Rodents

John W. Adams,1,2 David Unette,3 Todd Anthony,3 Joel Gaitlin,† Ibrahim Gaidarov2

1Arena Pharmaceuticals, Inc., San Diego, California, USA; 2Recon-Dx, San Diego, California, USA; 3Human Longevity, Inc., San Diego, California, USA

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