DEVELOPMENT OF THE NOVEL, PERIPHERALLY-SELECTIVE KAPPA OPIOID AGONIST CR665 FOR THE TREATMENT OF ACUTE PAIN

PM-015

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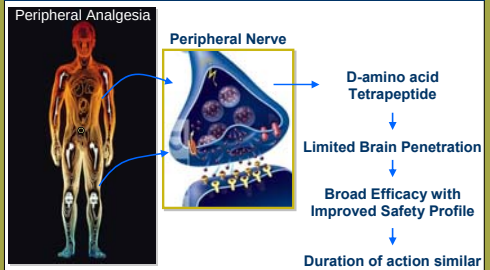
Introduction

The aversive cognitive effects caused by activation of kappa opioid receptors in the CNS (dysphoria, hallucinations) have hindered the development of compounds acting by this mechanism. However, activation of kappa receptors located outside of the CNS (peripheral nerve endings and immune cells including T-cells, macrophage, mast cells) appears sufficient to modulate the transmission of pain and inflammatory signals. Activation of kappa opioid receptors with kappa-selective agonists is also known to produce pharmacological effects that differ from activation of mu opioid receptors (e.g., no inhibition of GI transit, water retention, itch or induction of respiratory depression). Therefore, peripherally-restricted kappa agonists may represent a novel, better tolerated, class of anti-inflammatory and analgesic drugs for the treatment of acute and chronic pain.

Evidence from knockout mice suggest that kappa receptors play an important role in the modulation of visceral pain. Here we are presenting CR665, the clinical lead of our first generation of peripherally-acting kappa agonists as a novel approach for the treatment of acute visceral pain without the complications and side-effects of traditional opioid therapies.

Development of Peripherally-Restricted Kappa Agonists

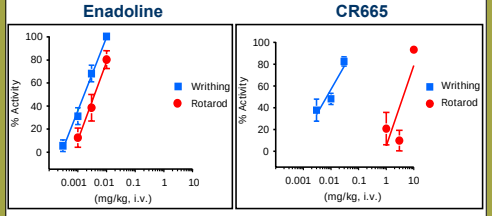


In Vitro Profile of CR665

Compound		hKOR (Ki, nM)	hMOR (Ki, nM)	hDOR (Ki, nM)
Peptide	**CR665**	**0.24**	**4050**	**20300**
Small molecules	Enadoline	1.25	272	707
	Asimadoline	0.17	581	322
	TRK-820	0.36	0.71	50
	Morphine	14.7	4.4	150

- ✓ Best-in-class non-narcotic opioids
- ✓ Full agonist (EC50 hKOR: 0.03 nM, cAMP assay)
- ✓ High affinity for both human and rodent KOR (rat Ki: 0.42 nM)
- ✓ No off-target activity on >94 receptors/channels/transporters

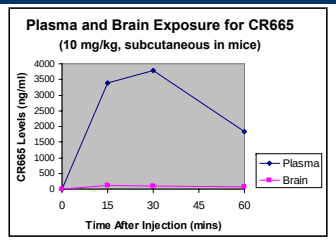
Peripheral Selectivity of CR665



	Writhing (A_{50}, mg/kg)	Rotarod (A_{50}, mg/kg)	Peripheral Selectivity
Enadoline	0.002	0.004	2
CR665	0.007	3.8	543

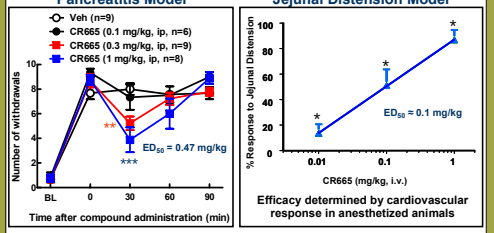
- ✓ 0.6% acetic acid induced writhing in male CD-1 mice
- ✓ CR665 IV has significantly larger therapeutic index compared to small molecule kappa agonists like Enadoline

Low Brain Penetration of CR665



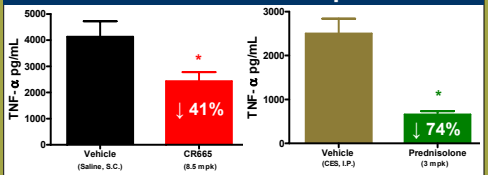
- ✓ Plasma half-life ranging from 1-2 hours across species
- ✓ Brain-to-Plasma Ratio less than 3%
- ✓ 70-85% Protein binding across species
- ✓ No oral bioavailability

Efficacy of CR665 in Rat Models of Visceral Pain



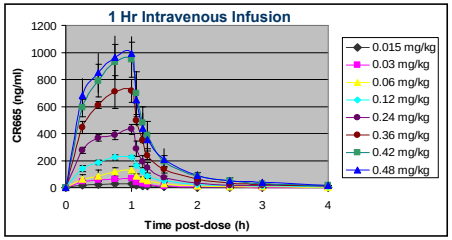
- ✓ CR665 is effective in multiple models of visceral pain including acetic-acid writhing, pancreatitis and jejunal distension

CR665 Suppresses TNFα Release in Mouse Model of Sepsis



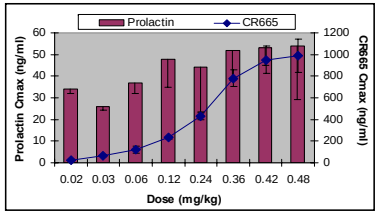
- ✓ LPS-induced cytokine release in female Balb/C mice
- ✓ Cytokine levels in serum measured by ELISA, 2 hr post-LPS
- ✓ Significant reduction in circulating TNFα levels following pre-treatment with CR665
- ✓ Suggests direct action of KOR on inflammatory cells

Pharmacokinetics of CR665 in Human



- ✓ Dose-proportionality increase in systemic exposure to CR665 with concentrations well above the estimated therapeutic concentrations in both male and female subjects
- ✓ Plasma half-life of 1-2 hours with rapid elimination

Pharmacodynamic Effect of CR665 on Release of Prolactin in Male Subjects



- ✓ Opioids including kappa agonists are known to induce release of Prolactin
- ✓ Activation of kappa receptors in anterior pituitary (outside of blood-brain barrier) likely involved
- ✓ Prolactin release observed at lowest dose tested (0.02 mg/kg) reaching a maximal effect at 0.12 mg/kg dose

Safety and Tolerability of CR665 in Human

Tolerability

- ✓ CR665 was well tolerated in both male and female healthy volunteers at dose levels through 0.42 mg/kg (1-h) and through 0.09 mg/kg (5-min)
- ✓ No severe or serious adverse effects (AEs) observed
- ✓ No report of hallucination, dysphoria or emesis
- ✓ Most frequently reported AEs were mild, transient nervous system symptoms (paresthesia, dizziness, somnolence)
- ✓ No treatment-related trends or significant clinical findings in serum biochemistry, haematology or urinalysis data
- ✓ No changes observed in serum electrolytes

Safety

- ✓ CR665 was determined to be safe at all doses and infusion rates tested (1 hr or 5-min infusion)

CR665 Attenuates Moderate Visceral Pain in Human Subjects

- ✓ CR665 was evaluated in a model of visceral pain in human subjects using esophageal distension (see PM-178)
  - ✓ Randomized, double-blind, double-dummy, active and placebo-controlled, cross-over study in 18 subjects
- ✓ CR665 (0.36 mg/kg,1 hr IV infusion) produced significant efficacy within a similar range as oxycodone (15 mg, oral) relative to placebo (double-dummy, IV and oral)
- ✓ CR665 was safe and well-tolerated with no significant AEs

Conclusions

- ✓ CR665 is potent and efficacious in a variety of rodent models of visceral pain, and inflammation
- ✓ Phase I study completed in normal healthy volunteers
  - ✓ CR665 was safe and well-tolerated
  - ✓ No evidence of dysphoria or hallucination
  - ✓ No evidence of Mu opioid related side effects
- ✓ CR665 has demonstrated efficacy for attenuating moderate visceral pain in humans (see PM-178)
- ✓ Efficacy in preclinical and human models suggest CR665 may be effective for the treatment of acute visceral pain
- ✓ Longer-acting and orally active kappa agonist CR845 also being developed for treatment of chronic inflammatory and neuropathic pain (see PW-231)

Acknowledgement

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