Preclinical Profile of CR845: A Novel, Long-Acting Peripheral Kappa Opioid Receptor Agonist

PW-231

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Introduction

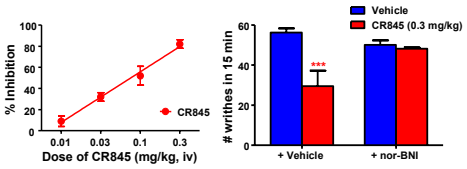
Extensive preclinical data support the role of kappa opioid receptors (KORs) in the modulation of itch, pain and inflammation. However, untoward effects caused by activation of KORs in the CNS (dysphoria, hallucinations) have hindered their development and thus has fueled the development of peripherally restricted KOR agonists. Previous generations of KOR agonists were aimed at maximizing oral exposure, consequently focusing on small heterocyclic molecules. Unfortunately, the chemical properties which facilitate gut absorption are also likely to result in CNS penetration. Our approach focused on the development of D-amino-acid tetrapeptides as a mean to limit CNS penetration with CR665 as the clinical lead of our first-generation of peripherally acting kappa agonists. CR665 was shown to be well tolerated in human subjects, with no reports of dysphoria or hallucinations (Menzaghi *et al.*, #PM-015) and was as effective as oxycodone in a human experimental model of acute visceral pain (Arendt-Nielsen *et al.*, #PM-178). CR665 was tested as an intravenous formulation. It is amenable to patch formulation but it is not orally bioavailable. We have therefore developed a second generation of peripherally-acting kappa agonists with oral activity. Here we are presenting the broad preclinical properties of CR845, our new clinical lead.

In Vitro Profile of CR845

Compound		hKOR (Ki, nM)	hMOR (Ki, nM)	hDOR (Ki, nM)
Peptides	**CR845**	**0.32**	**>10000**	**>10000**
	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

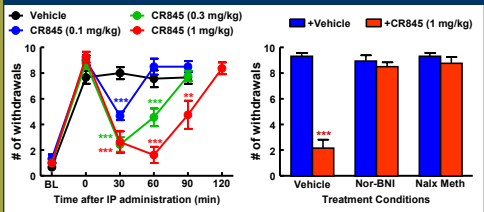
- ✓ **Best-in-class non-narcotic opioids**
- ✓ **Full agonist; EC_{50} = 0.16 nM (cAMP assay)**
- ✓ **High affinity for both human and rodent KOR**
- ✓ **No off-target activity on >94 receptors/channels/transporters**

CR845 Inhibits Writhing Behavior in Mice With an 18 hr Duration of Action



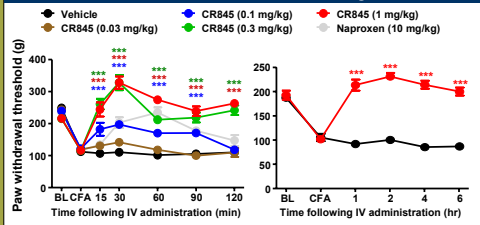
- ✓ **0.6% acetic acid induced writhing in male CD-1 mice**
- ✓ **CR845 ED_{50} = 0.07 mg/kg IV (0.06-0.10; 95% CI) @ 15 min**
- ✓ **CR845 retains 57% activity 18 hr after an ED_{80} dose**
- ✓ **Efficacy at 18 hr reversed by nor-BNI treatment suggesting efficacy is KOR mediated**

CR845 Alleviates Abdominal Pain in a Rat Model of Persistent Pancreatitis



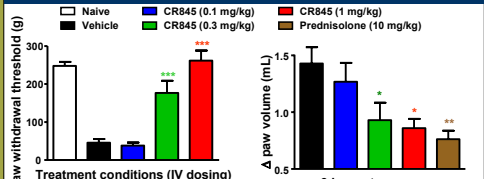
- ✓ **DBTC-induced pancreatitis in male SD rats**
- ✓ **Response to probing abdomen with Von Frey filament (4g)**
- ✓ **ED_{50} = 0.3 mg/kg IP (0.2-0.4; 95% CI) @ 60 min**
- ✓ **Efficacy blocked by either nor-BNI or naloxone methiodide suggesting efficacy is mediated by peripheral KORs**

CR845 Alleviates Hyperalgesia in a Rat Model of Inflammatory Pain



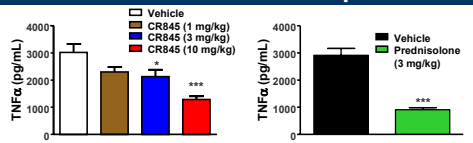
- ✓ **CFA-induced inflammatory pain in male SD rats (50 µg).**
- ✓ **Response to noxious mechanical stimulus (Randall-Selitto)**
- ✓ **ED_{50} = 0.3 mg/kg IV (0.2-0.4; 95% CI) @ 60 min**
- ✓ **Duration of action > 6hr**

CR845 Inhibits Carrageenan-induced Hind Paw Edema in Rats



- ✓ **0.1 mL of 2% carrageenan intraplantar to male SD rats**
- ✓ **Response to noxious mechanical stimulus (Randall-Selitto)**
- ✓ **Hind paw volumes were obtained using a plethysmometer**
- ✓ **CR845 MED = 0.3 mg/kg, IV**

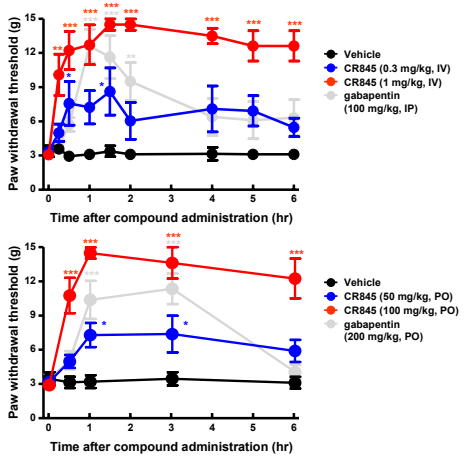
CR845 Suppresses Cytokine Release in Mouse Model of Sepsis



Cytokine	Prednisolone % reduction	CR845 % reduction
TNFα	64%	47%
IL-1β	39%	26%
IL-2	24%	23%
MIP-1β	19%	19%
IL-12 (p40/p70)	45%	23%

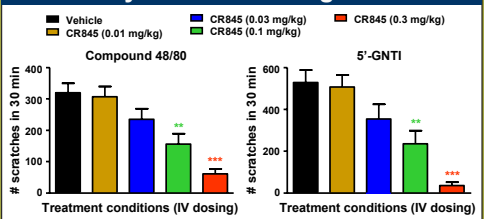
- ✓ **LPS-induced cytokine release in female Balb/C mice**
- ✓ **Cytokine levels in serum measured by luminex, 2 hr post-LPS**
- ✓ **CR845 MED = 3 mg/kg, SC on TNFα release**
- ✓ **Suggests direct action of KOR on inflammatory cells**

CR845 Inhibits Tactile Hypersensitivity in a Rat Model of Neuropathic Pain



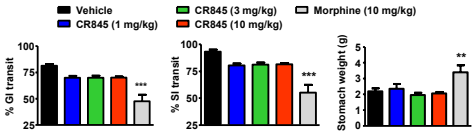
- ✓ **L_5/L_6 spinal nerve ligation (Chung model) in male SD rats**
- ✓ **Response to probing injured paw with von Frey filaments**
- ✓ **CR845 ED_{50} = 0.38 mg/kg (0.31-0.45; 95% CI), IV**
- ✓ **Orally active with a duration of action > 6 hr**

CR845 Inhibits Scratching Behavior Elicited by Known Pruritogens in Mice



- ✓ **Compound 48/80 or 5'GNTI induced pruritus in male SW mice**
- ✓ **Number of scratches counted over a 30 min period**
- ✓ **CR845 ED_{50} ≤ 0.08 mg/kg IV (0.06-0.12; 95% CI)**
- ✓ **Efficacy comparable to TRK-820**

CR845 Does Not Produce Untoward Gastrointestinal Side Effects in Rats



- ✓ **Unlike morphine, CR845 does not alter gastrointestinal transit or gastric emptying suggesting low potential for constipation**

Conclusions

- ➢ **CR845 is potent and efficacious in a variety of rodent models of itch, pain, and inflammation**
  - ✓ **Visceral pain (writhing, pancreatitis)**
  - ✓ **Inflammatory pain (carrageenan, Freund's adjuvant)**
  - ✓ **Neuropathic pain (Chung model)**
  - ✓ **Evoked itch (compound 48/80 and GNTI)**
- ➢ **Phase I trial**
  - ✓ **Single escalating IV dose study completed in 54 normal healthy volunteers; safe and well-tolerated at all doses tested**
  - ✓ **No evidence of serious adverse effects or adverse CNS activity at plasma levels of drug expected to be associated with clinical efficacy**
  - ✓ **Oral formulation under development**
- ➢ **Phase IIa, IV formulation – POC studies planned (Q4 '08)**

Acknowledgement

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