An opioid-neurotensin hybrid peptide outperforms morphine in acute and chronic pain models

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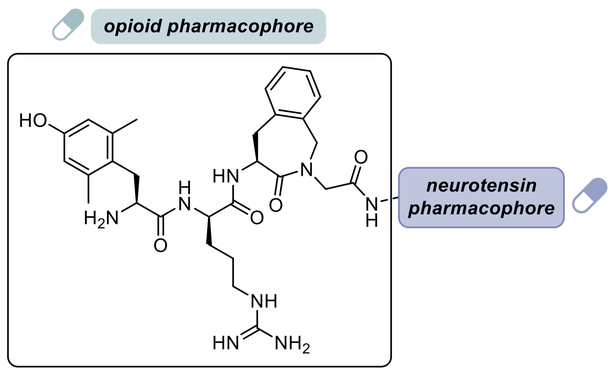
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Abstract

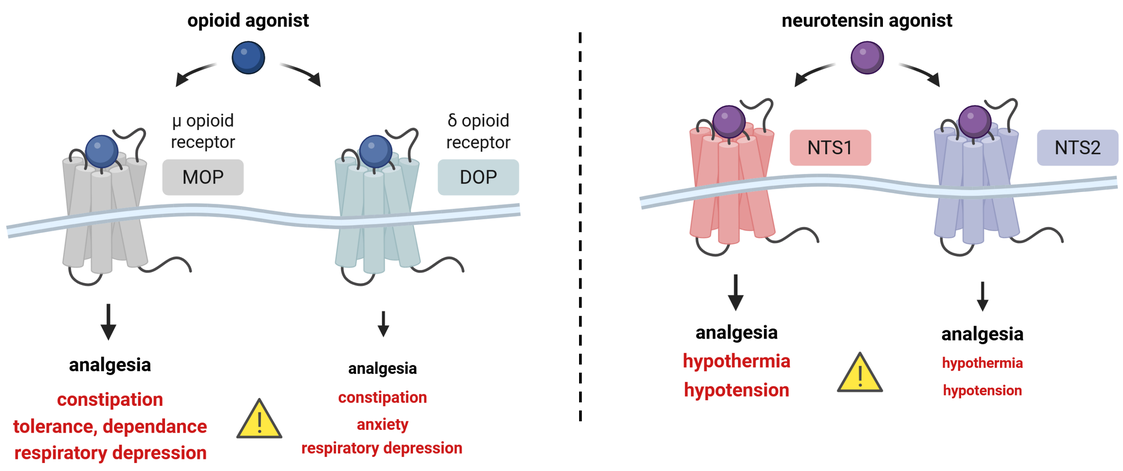
Best of both worlds:

- ***More potent than morphine***
  in acute & chronic pain models
- ***Prolonged effect***
- ***Reduced side effects***

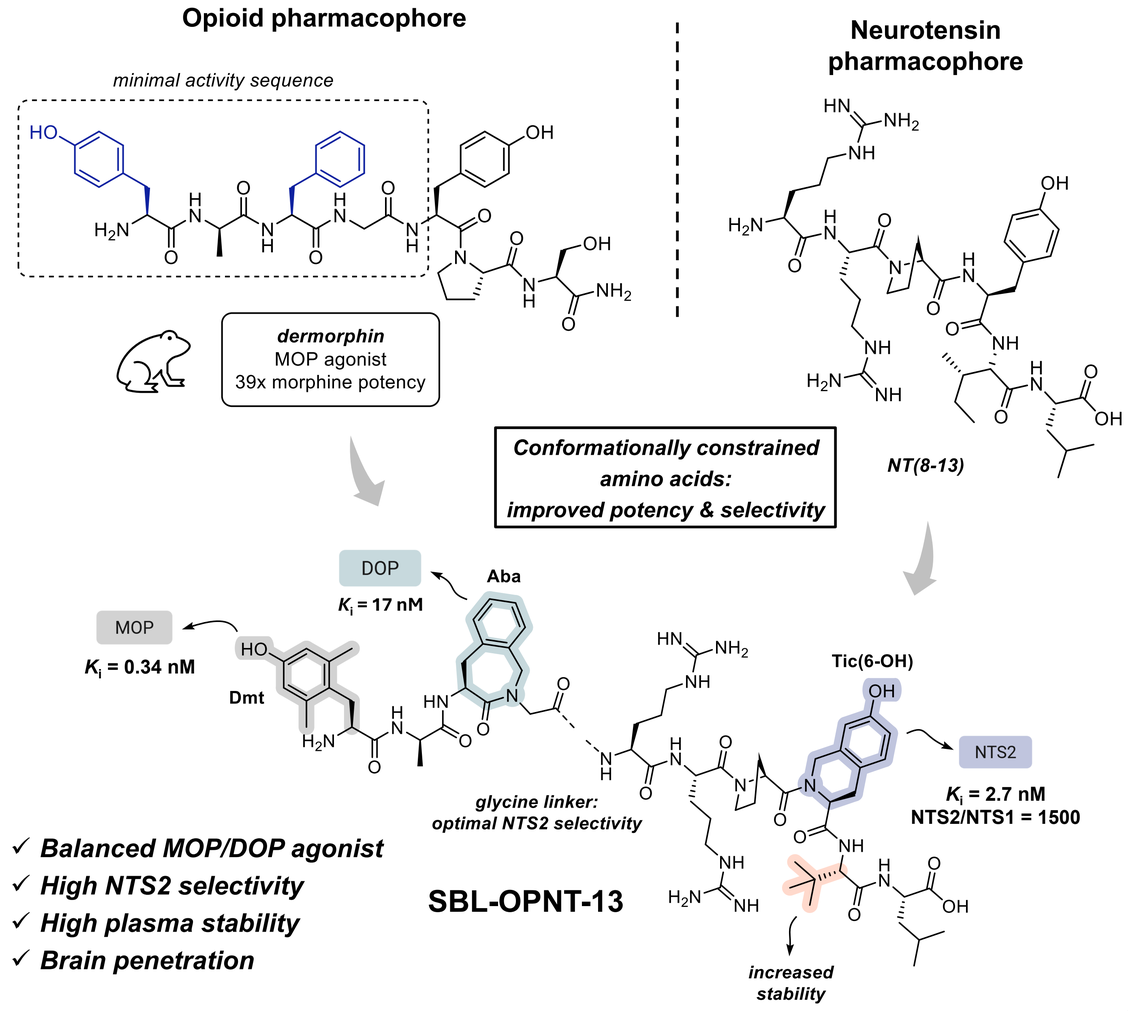
⇒ **Safer analgesic profile**



Opioid and neurotensin receptors[1]

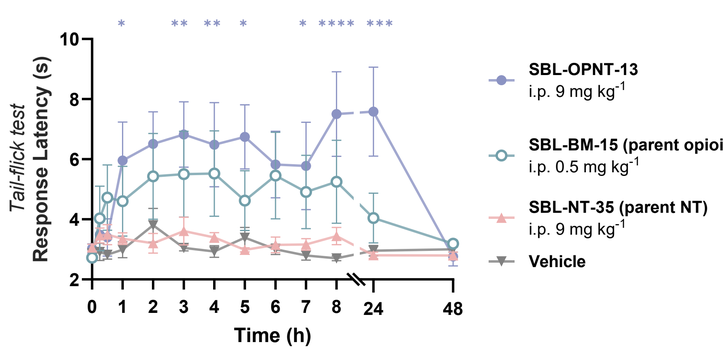


Lead peptide design[2,3]



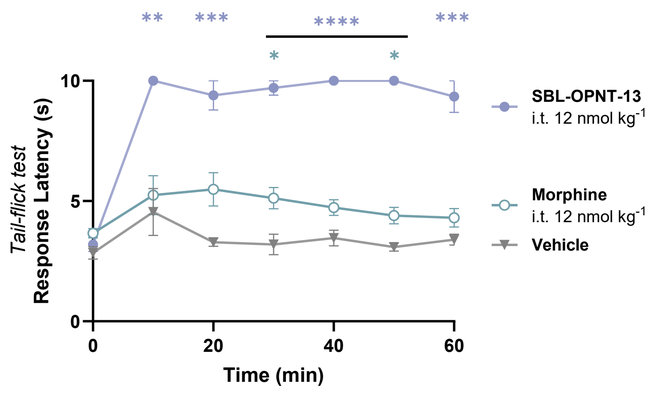
Preclinical efficacy[4]

The hybrid peptide outperforms the parent moieities



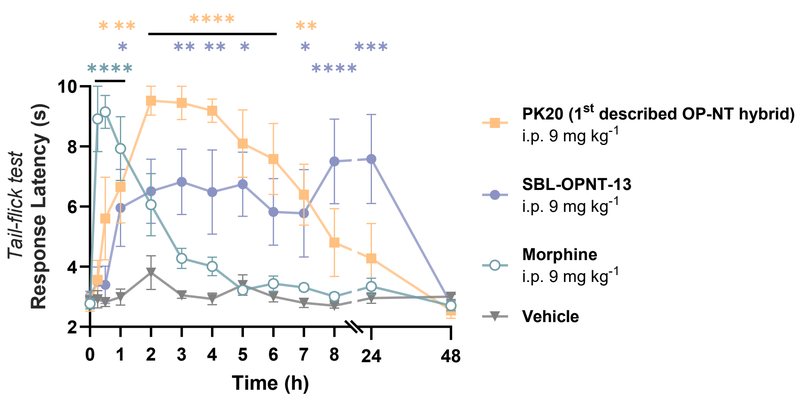
n = 5-6

Efficacy in acute pain model



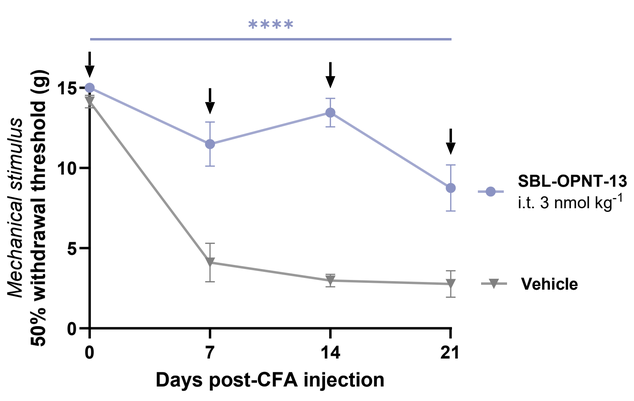
n = 6

Sustained analgesia >24 hours



n = 5-6

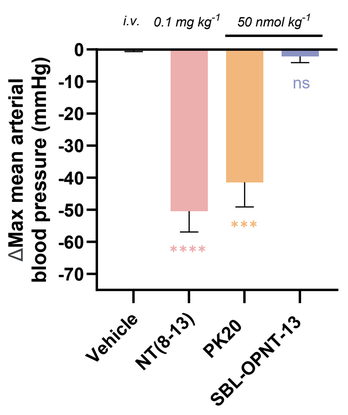
Efficacy in chronic pain model



n = 6

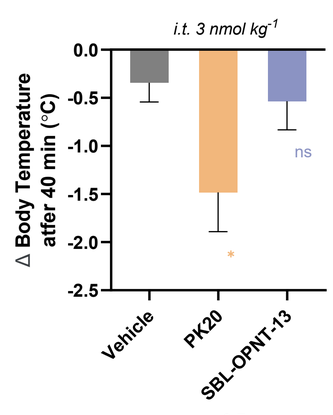
Adverse effects[4]

Hypotension



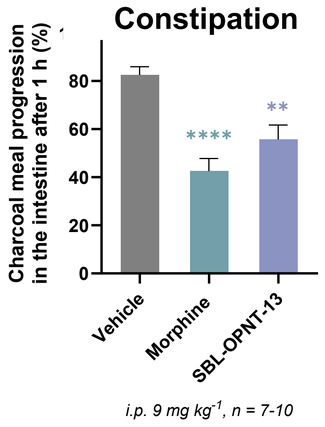
n = 6

Hypothermia



n = 6-7

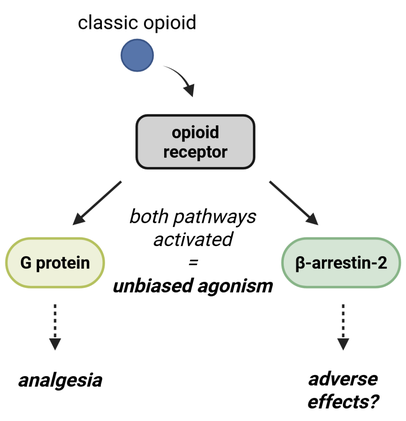
Constipation

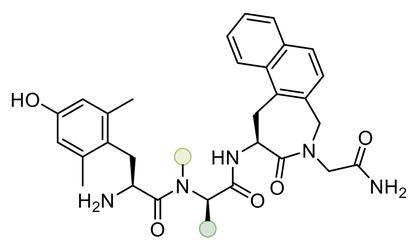


i.p. 9 mg kg-1, n = 7-10

- ✓ ***No NTS1-related hypotension***
- ✓ ***No NTS1-related hypothermia***
- × ***Opioid-related constipation still observed***
- × ***Opioid tolerance still observed***

Perspectives: biased opioid agonism[5]





Mechanistic studies & therapeutic perspectives

Charge vs. no charge	*N*-Sustitution	β-Arrestin-2 max. efficacy
D-Ala	H	94 ± 6%
D-Arg	H	50 ± 3 %
D-Arg	Me	25 ± 1 %
D-Arg	Pr	7 ± 4 %

Conclusions

- **SBL-OPNT-13** is potent in preclinical acute and chronic pain models
- High NTS2 selectivity prevented neurotensin-related side effects
- Opioid-related side effects remain challenging to understand and address

References

1. Breault *et al.*, *Pharmacol. Res.* **2024**, *209*, 107408.
2. Gonzalez *et al.*, *J. Med. Chem.* **2020**, *63* (21), 12929–12941.
3. De Neve *et al.*, *ACS Pharmacol. Transl. Sci.* **2024**, *7* (9), 2784–2798.
4. Breault *et al.*, *Biomed. Pharmacother.* **2026**, *199*, 119488.
5. De Neve *et al.*, unpublished data.

More information

Acknowledgements

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