Preclinical development of novel kappa opioid compounds for the treatment of drug-addiction

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No approved pharmacotherapies for treatment of psychostimulant addiction
Kappa opioid systems & Addiction

Dynorphin mRNA

Normal

Cocaine User

Hurd and Herkenham, 1993
Co-Localization of KOPr and DAT

Kappa opioids regulate Dopamine levels

Svingos et al., 2001

Chefer et al., J Neuroscience (2005)
KOPr Agonists Exert ‘Cocaine-Antagonist’ Like Effects in Animal Models of Drug-Seeking

- Attenuates i.v. cocaine self-administration
- Attenuation of cocaine—prime induced cocaine-seeking in animal models of relapse
- Attenuation of cocaine induced hyperactivity

*Schenk S, Partridge B, Shippenberg TS (1998-2001)*
Modified analogues

Salvia divinorum

Modified C2 analogue

Salvinorin A

EC$_{50}$: 0.030 nM
ANTI-ADDICTION EFFECTS

Cocaine prime-induced reinstatement

#2
C16 analogue

#1
C16 analogue

C2 Analogue
LONGER DURATION OF ACTION

Tail withdrawal assay
SIDE EFFECTS

Sedation: Locomotor activity

*Figure showing bar graphs for Vehicle and Novel analogue with different C16 and C2 Analogue groups.*

#2 C16 analogue

#1 C16 analogue

C2 Analogue
SIDE EFFECTS

Aversion: Conditioned place aversion

#1
C16 analogue

C2 Analogue
SIDE EFFECTS

Depression: Forced swim test (FST)

Climbing: Vehicle, novel analogue, Vehicle, novel analogue, Vehicle, novel analogue
Swimming: Vehicle, novel analogue, Vehicle, novel analogue, Vehicle, novel analogue
Immobility: Vehicle, novel analogue, Vehicle, novel analogue, Vehicle, novel analogue

#1 C16 analogue
C2 Analogue
SIDE EFFECTS

Anxiety: Light/Dark test

![Graph showing time in light box (s) for different treatments including vehicle, Salvinorin A, #2 C16 analogue, #1 C16 analogue, C2 analogue. The graph displays statistical significance markers (**).]
Conclusions

Analogues of Salvinorin A hold promise for the development of anti-addiction pharmacotherapies

- All Longer acting
- Fewer side effects

- All have anti-cocaine effects (decrease drug-seeking)
- No sedative effects observed
- #1 C16 analogue has no pro-depressive effects or anxiety effects
  - But shows aversion
- C2 analogue has no anxiety effects or aversion but has pro-depressive effects
- #2 C16 analogue has highest efficacy in drug-seeking tests but side effects need to be fully evaluated
ACKNOWLEDGEMENTS:

David Young
Amy Ewald
Aimee Culverhouse
Nitin Kumar
Bridget Simonson
Aashish Morani

Prof. Thomas Prisinzano
& Andrew Riley
University of Kansas