Allosteric modulation of the type 1 cannabinoid receptor for the treatment of Huntington’s disease

April 6 2018 – Cannabinoids in Clinical Practice

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Huntington’s disease

When I grow up, my mind and body will slowly deteriorate until I choke to death trying to swallow.
HD and CB1R

One of the earliest changes in gene expression that occurs during the development of HD is a decrease in the level of CB1R

HD and CB1R

- HD x CB1R\(^{-/-}\) mice progress into HD symptoms earlier and display more severe symptoms than HD x CB1R\(^{+/+}\) mice

- Rescue of CB1R expression with adeno-associated virus reduces signs and symptoms of HD mice

CB1R levels decrease in HD patients

***$P < 0.001$ compared to Control

Laprairie et al. (2014) J Neuroimmunol
Is there a way to maintain function or increase levels of CB1R in HD pharmacologically?
In theory: reduced likelihood for dependence, tolerance, adverse effects because the drug is only effective in the presence of an orthosteric ligand.

Wooten et al. (2013) Nat Rev Drug Discov
CB1R allosteric modulators

ORG27569 and PSNCBAM-1:
Synthetic CB1R NAMs
Orthosteric inverse agonist effects

Lipoxin A₄:
Endogenous, unstable CB1R PAM
Novel CB1R allosteric modulators

- 200 compounds synthesized by Dr. Ganesh Thakur
- NAMs range in potency from low – high nM
- PAMs range in potency from mid – high nM
- Ligand bias: some are 40-fold more-selective for one pathway over another

Independent validation:
- $^{35}$S GTPγS and $^3$H CP55,940 (University of Aberdeen)
- Electrophysiology (Indiana University)
GAT211: synthetic CB1R PAM

Laprairie et al. (2017) ACS Chem Neurosci
GAT228 and GAT229 *in vitro*.

Laprairie *et al.* (2017) ACS Chem Neurosci
Despite a large body of literature on CB1R, CB1R and structure-activity relationships (SAR) were limited by existing scaffolds from natural sources.
Applying CB1R PAMs to disease

A CB1R PAM (GAT229) could enhance endocannabinoid activity and provide benefit in HD and other disease state.
GAT211 and GAT229 normalized CB1R levels in R6/2 HD mice.

***$P < 0.001$ vs. C57Bl/6J, ^^^$P < 0.001$ vs. vehicle

Laprairie et al. – Neurobiol Dis (in review)
GAT211 and GAT229 reduced symptom severity in R6/2 HD mice.

***P < 0.001 vs. 211 (black) or 229 (red)

Laprairie et al. – Neurobiol Dis (in review)
GAT211, 228, and 229 altered metabolism in R6/2 HD mice.

* $P < 0.01$ vs. C57Bl/6J, ^$P < 0.01$ vs. vehicle

Laprairie et al. – *Neurobiol Dis* (in review)
Conclusions

- CB1R PAMs that enhance endocannabinoid signaling may be useful in treating HD at the:
  - Intra- and interneuronal,
  - Behavioural and phenotypic, and
  - Metabolic levels

- The newly resolved crystal structures of hCB1R will allow for improved rational drug design.
Big questions and future work

• The Cannabinoid Research Initiative of Saskatchewan (CRIS)
  • CARE-E expansion
  • Future clinical projects

• CB1R PAMs in other disease states:
  • the GAERs rat (Absence epilepsy)
  • EAE mice (Multiple sclerosis)

• Structure-activity relationships of CB1R allosteric modulators
  • \textit{in vitro, in vivo}
  • PET development
Acknowledgements

Mariam Alaverdashvili
John Howland
Andrew Roebuck
Quentin Greba

Eileen Denovan-Wright
Melanie Kelly
Amina Bagher
Jillian Rourke

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