Knockout Models and Buprenorphine for the Clinician

Eric Prommer, MD FAAHPM, HMDC UCLA School of Medicine

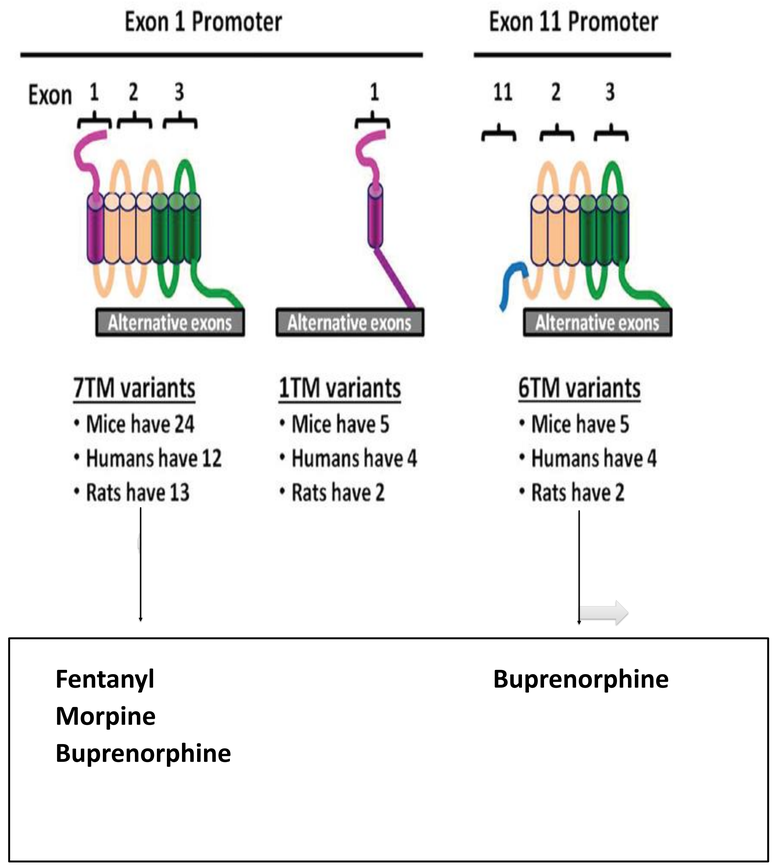
Introduction

The mu opioid receptor gene has distinct promoters and undergoes extensive splicing generating 3 classes of splice variants with differing interactions with are currently available opioids.

The existence of multiple mu opioid receptors has been suggested by clinical manifestations such as interindividual differences in opioid responsiveness and adverse effects. One hypothesis to address these questions is that the single copy of the OPRM1
gene creates multiple mu-opioid receptor splice variants or isoforms through alternative pre-mRNA splicing

Research has now identified important variants. the OPRM1 splice variants can be categorized into three main types as indicated in the diagram.

Results



Conclusions

Buprenorphine interacts with both 7TM variants And 6TM variants of the mu opioid receptor.

Buprenorphine's analgesic effects depend on both the 7TM and 6TM variants.

Buprenorphine exhibits attenuated analgesia in exon 1 knockout mice(no 7TM)

Exon 11 knockout mice(no 6TM) completely eliminates buprenorphine analgesia

In genetic models disrupting ORL, delta , kappa does not disrupt buprenorphine analgesia

New opioids have been discovered which interact with 6TM only. Drugs such as 3-Iodobenzoylnaltrexamide 1 (IBNtxA) interact only with 6TM and are the future of opioids.

References

1.Grinnell, S. G., Ansonoff, M., Marrone, G. F., Lu, Z., Narayan, A., Xu, J.& Pasternak, G. W. (2016). Mediation of buprenorphine analgesia by a combination of traditional and truncated mu opioid receptor splice variants. *Synapse*, *70*(10), 395-407.

2, Majumdar, S., Subrath, J., Le Rouzic, V., Polikar, L., Burgman, M., Nagakura, K., Pasternak, G. W. (2012). Synthesis and evaluation of aryl-naloxamide opiate analgesics targeting truncated exon 11-associated μ opioid receptor (MOR-1) splice variants. *Journal of medicinal chemistry*, *55*(14), 6352-6362.