Opioid peptides induce long-term depression at glutamatergic synapses in the dorsal striatum

Brady K. Atwood & David Lovinger
National Institute on Alcohol Abuse and Alcoholism, Rockville, MD, USA

Abstract

The dorsal striatum is a brain region that is critically involved in action selection and habit formation and as such plays an important role in addiction to drugs of abuse. Opioid peptides and their receptors are abundantly expressed in this brain region. Many components of this endogenous opioid system in the striatum are modulated by drugs of abuse, suggesting that the opioid system is a possible a critical component of the machinery involved in addiction. There is a paucity of data concerning opioid roles in long-term synaptic plasticity in the dorsal striatum. We are also in the process of determining what effects both acute and chronic exposures to opioids that mediate this LTD is an ongoing effort. We are also discovering that this inhibition is long-lasting and is able to be blocked, but not reversed by opioid receptor antagonists, suggesting that this is opioid-induced long-term depression (LTD). We also found that intra-striatal stimulation coupled with a brief application of peptidase inhibitors also produced LTD that could be blocked by opioid receptor antagonists. Determining the identity of the endogenous opioids that mediate this LTD is an ongoing effort. We are also in the process of determining what effects both acute and chronic exposures to opioids have on opioid LTD. These data demonstrate a novel form of long-lasting synaptic plasticity in the dorsal striatum that is induced by at least a brief in vitro exposure to opioid peptides.

Methods

Coronal brain slices containing the striatum were made from Sprague Dawley rats (age P11-P19; Figs. 1-6) or C57BL/6J mice (age P15-P30; Fig. 7). Whole cell patch clamp recordings were made from medium spiny neurons of the dorsal striatum. Neurons were held at -40 mV and stimulated every 20 seconds. Drugs were administered via bath application following a 5-10 minutes baseline period. 50 µM picrotoxin was added to artificial CSF to isolate excitatory transmission.

Conclusions

1. Opioid receptor activation in the dorsal striatum produces long-term depression of excitatory transmission (OP-LTD).
2. OP-LTD can be induced by increasing locally produced endogenous opioid peptides.
3. mu-OP-LTD, but not delta-OP-LTD occludes endocannabinoid-mediated LTD.
4. Induction of mu-OP-LTD can be prevented by a prior in vivo injection of oxycodone.

Results

Figure 1: Mu opioid receptor activation produces long-term depression of excitatory transmission in dorsal striatum.

CTAP blocks, but does not reverse the long-lasting inhibition of EPSCs produced by DAMGO. MOP-LTD is expressed presynaptically as DAMGO increases the PPR and decreases the frequency of sEPSCs without changing sEPSC amplitude.

Figure 2: Delta opioid receptor activation produces long-term depression of excitatory transmission in dorsal striatum.

DAMGO blocks, but does not reverse the inhibition produced by met-enkephalin whereas CTAP (5 µM) is ineffective. Dynorphin A is completely blocked by nor-binaltorphimine (0.1 µM) and partially by CTAP (1 µM). Neither nor-BNI or CTAP reverses the effects of dynorphin A.

Figure 3: Kappa opioid receptor activation produces long-term depression of excitatory transmission in dorsal striatum.

Peptidase inhibitors produce long-lasting inhibition of EPSCs produced by DPDPE. DOP-LTD is expressed similarly to MOP-LTD (Figure 1).

Figure 4: Bath application of endogenous opioid peptides produces long-term depression of excitatory transmission in dorsal striatum.

Both met-enkephalin and dynorphin A produce long-lasting inhibition of EPSCs. Naltrindole (1 µM) blocks, but does not reverse the inhibition produced by met-enkephalin whereas CTAP (5 µM) is ineffective. Dynorphin A is completely blocked by nor-BNI (1 µM) and partially by CTAP (1 µM). Neither nor-BNI or CTAP reverses the effects of dynorphin A.

Figure 5: Local production of endogenous opioid peptides in the dorsal striatum suppresses excitatory transmission.

Peptidase inhibitors produce long-lasting inhibition that is completely blocked by 2 µM naloxone or 1 µM CTAP and partially blocked by 1 µM naltrindole or 0.1 µM nor-BNI. Naloxone does not reverse the endogenous opioid-LTD. This LTD is expressed presynaptically. Peptidase inhibitor effects require local electrical stimulation in order to produce EPSC suppression.

Figure 6: MOP-LTD and DOP-LTD differ in their ability to occlude endocannabinoid-mediated LTD and each other.

100 Hz stimulation for 1 second (4 times every 10 sec) combined with depolarization to 0 mV induces endocannabinoid LTD. eCB-LTD does not occlude MOP-R LTD or DOP-R LTD. MOP-R LTD, but not DOP-R LTD occludes eCB-LTD. DOP-R LTD partially occludes MOP-R LTD, but not vice versa.

Figure 7: A single in vivo exposure to oxycodone prevents the induction of mu opioid receptor long-term depression in the dorsal striatum. 1 mg/kg oxycodone or saline was injected into C57BL/6J mice and brain slices were made 1 hr. later. Recordings were performed 2-7 hours later. In mice injected with saline, oxycodone, DAMGO and DPDPE produce OP-R LTD. In mice injected with oxycodone, oxycodone and DAMGO fail to produce synaptic depression. DPDPE-mediated inhibition is unaffected.