Orexin/Hypocretin enhances synaptic strength in VTA dopamine neurons

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Orexin/Hypocretin and Reward

- Orexin/Hypocretin increases VTA neuron firing (Korotkova et al., 2003)
- Intra-VTA orexin/hypocretin increases dopamine in the Nucleus Accumbens (Narita et al., 2006) or PFC (Vittoz and Berridge, 2006)
- Orexin/Hypocretin neurons are activated when rats prefer morphine in a CPP paradigm which is blocked by intra VTA hypocretin antagonist (Harris et al., 2005)
- CPP for morphine is abolished in orexin/hypocretin peptide knockout mice (Narita et al., 2006).
- Orexin/hypocretin i.c.v. reinstates cocaine seeking (Boutrel et al., 2006)

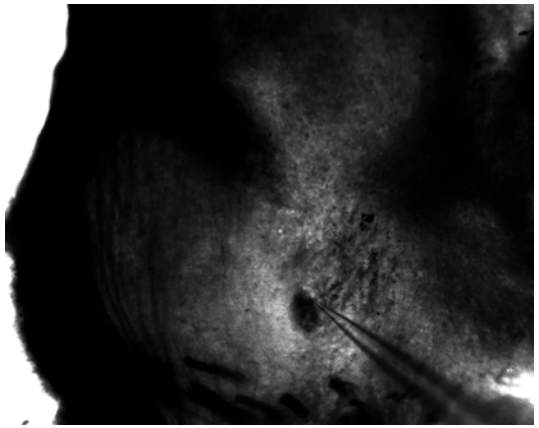
How does orexin/hypocretin mediate the rewarding effects of drugs?

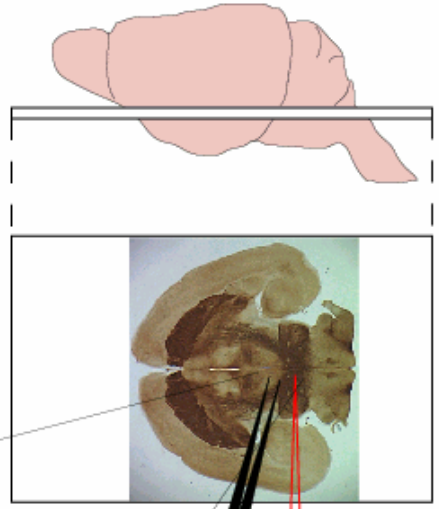
Can ox/hcrt cause synaptic plasticity in dopamine neurons?

Why is synaptic plasticity in the VTA important?

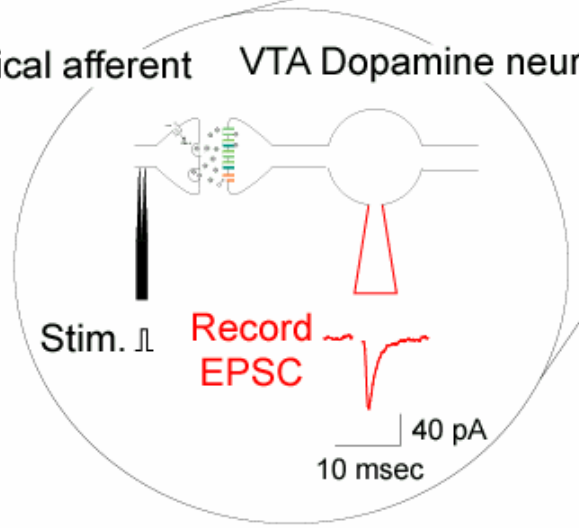
- Glutamatergic synaptic plasticity plays a key role in neural plasticity relevant to addiction
  - Induction of behavioral sensitization is dependent on activation of NMDA receptors in the VTA (Kalivas and Alesdatter, 1993)
- Synaptic plasticity of dopamine neurons in the VTA may play a key role in the reinforcement of reward.

Patch Clamp Recording from VTA neurons





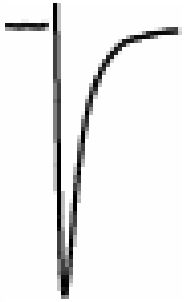
NMDA EPSC
+40 mV



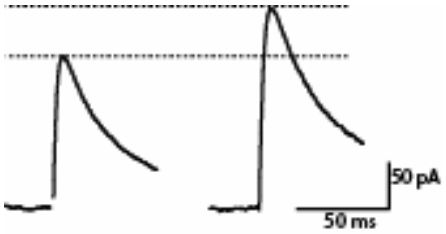
Stim. Record EPSC

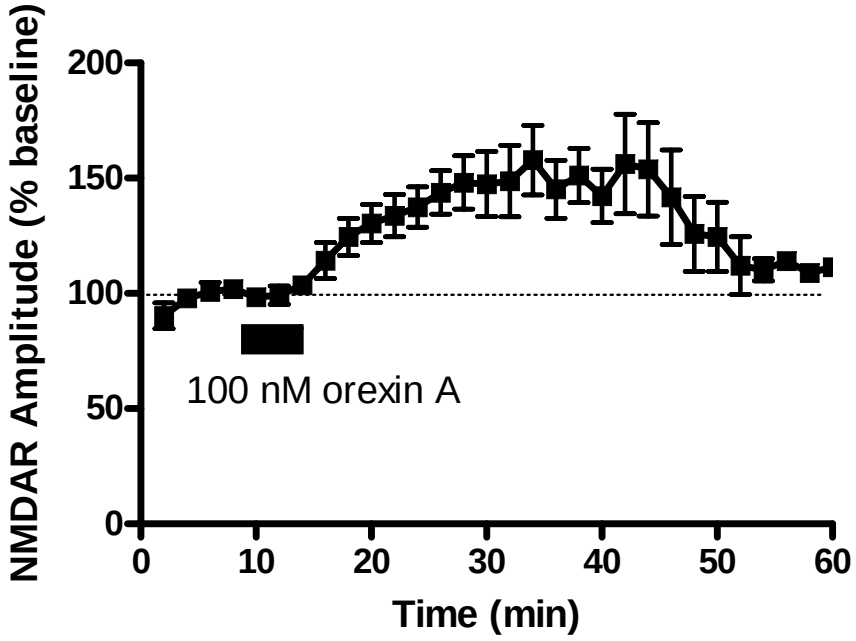
(Excitatory Postsynaptic **Currents**)

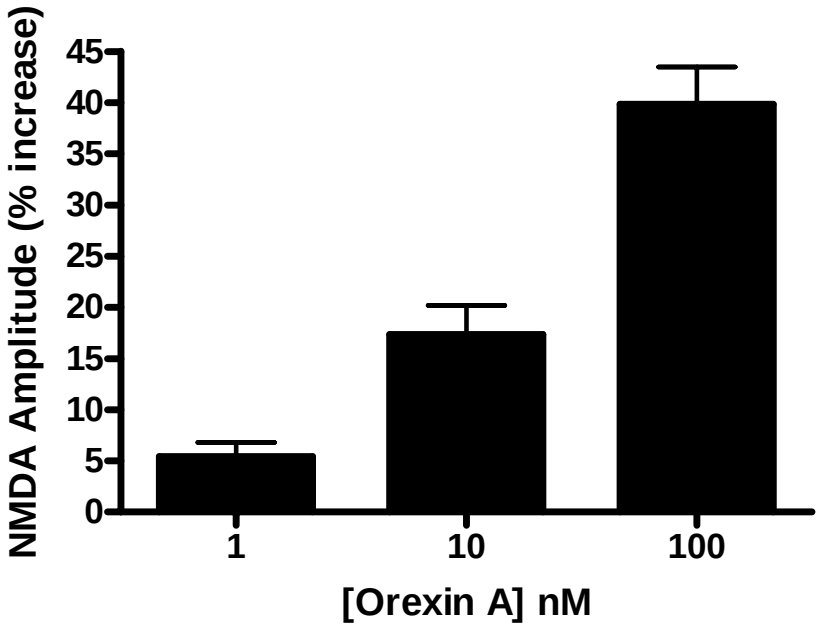
AMPA EPSC
-70 mV



OxA/Hcrt1 concentration-dependently increases NMDAR EPSCs in VTA neurons

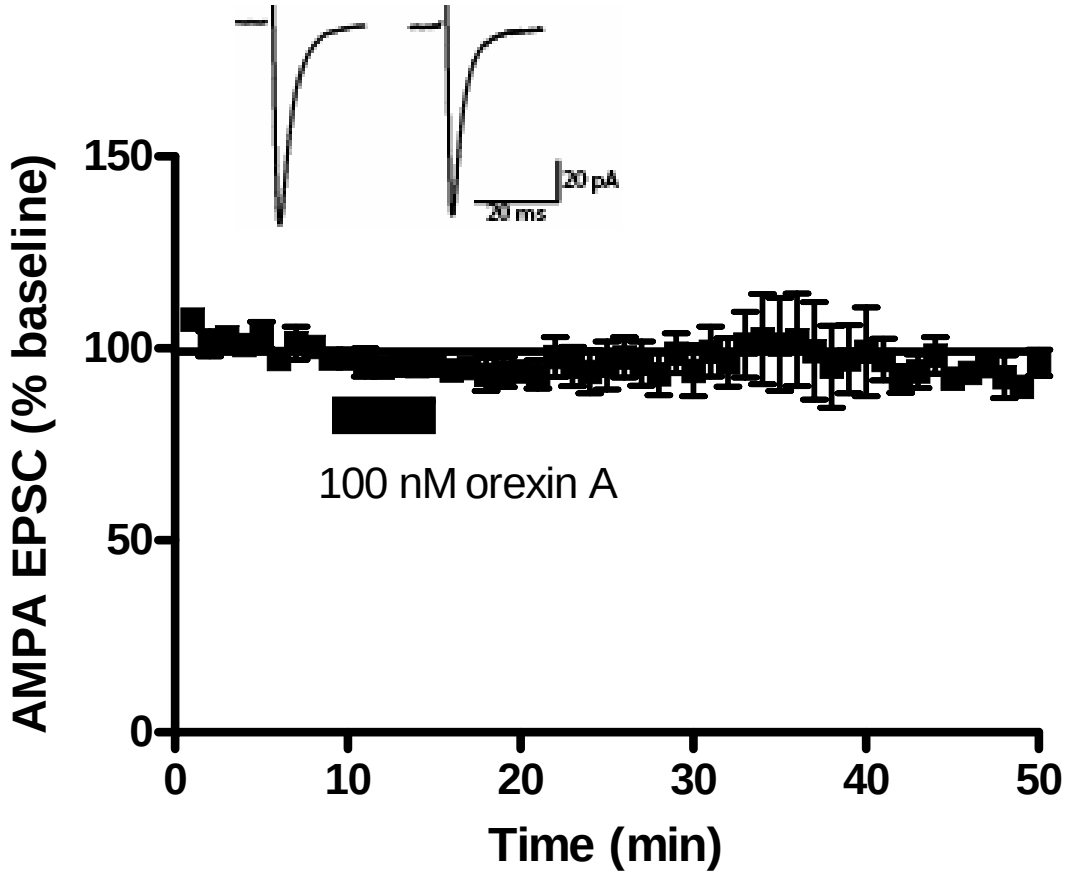






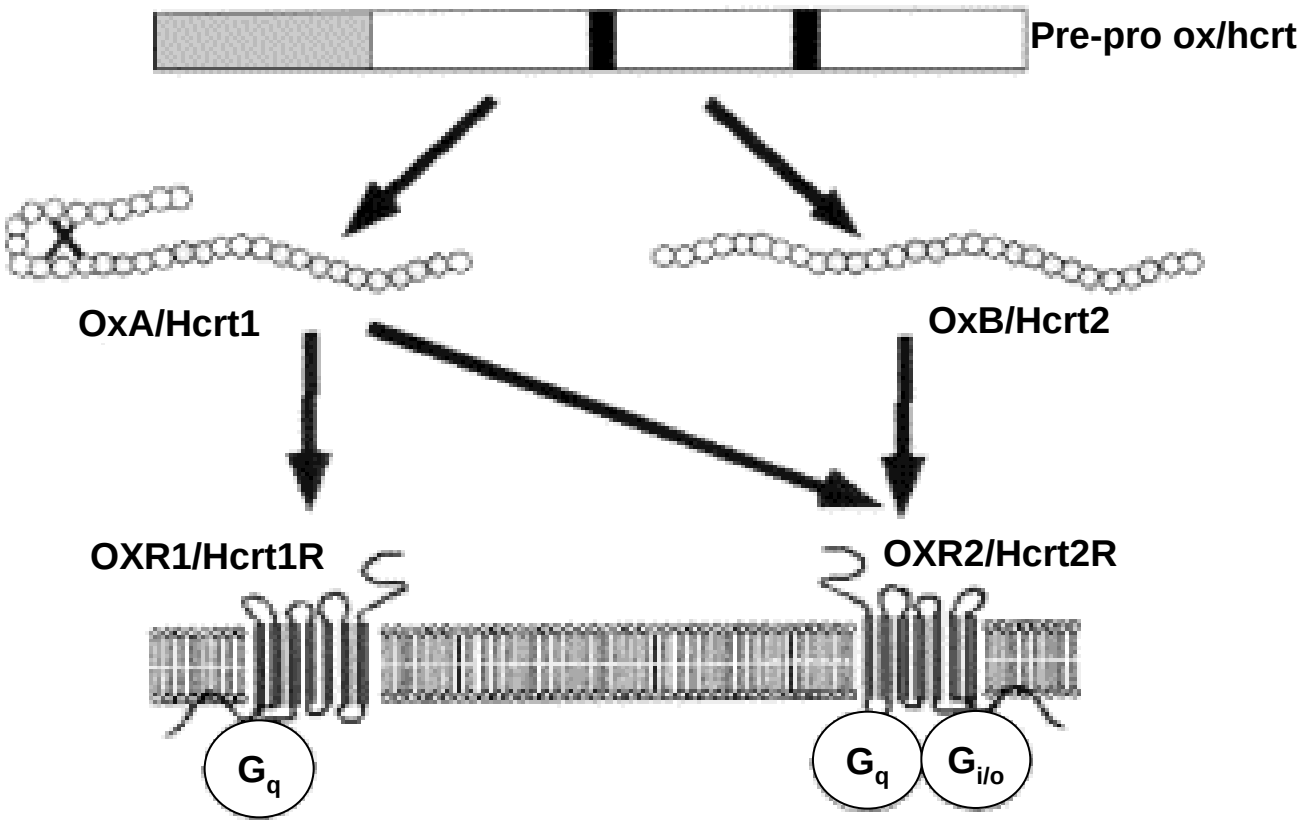
n=12

OxA/Hcrt1 does not potentiate AMPA EPSCs in VTA neurons

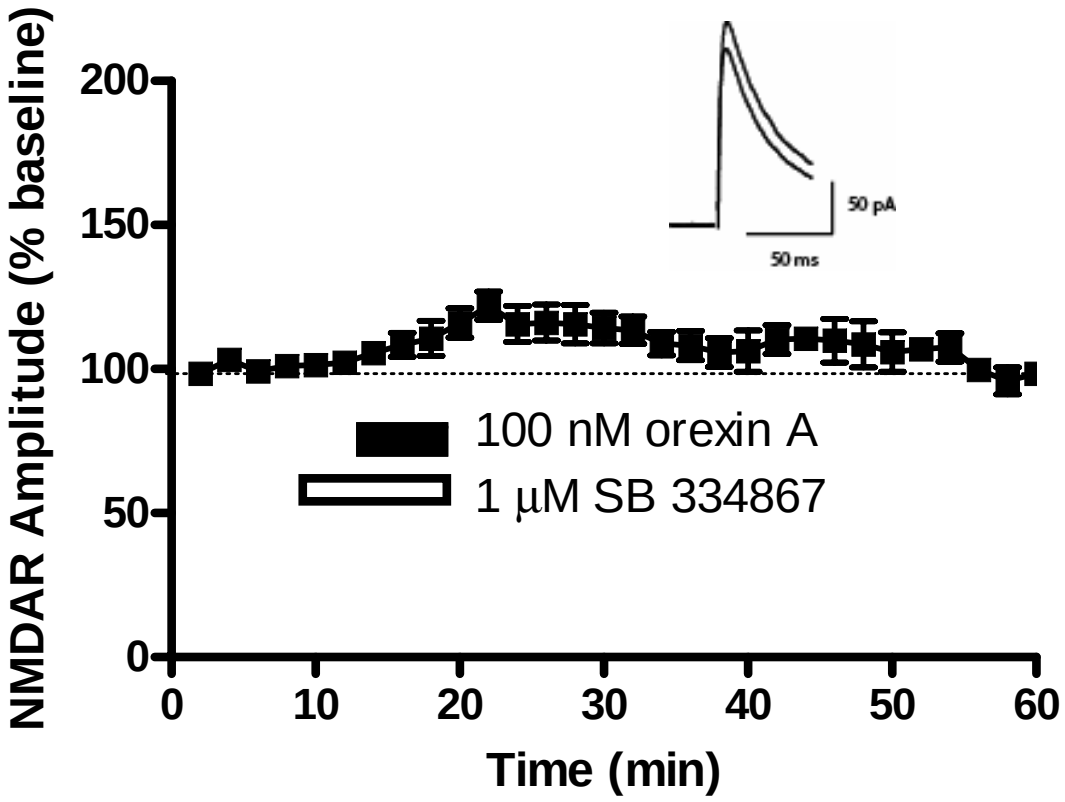


n=8

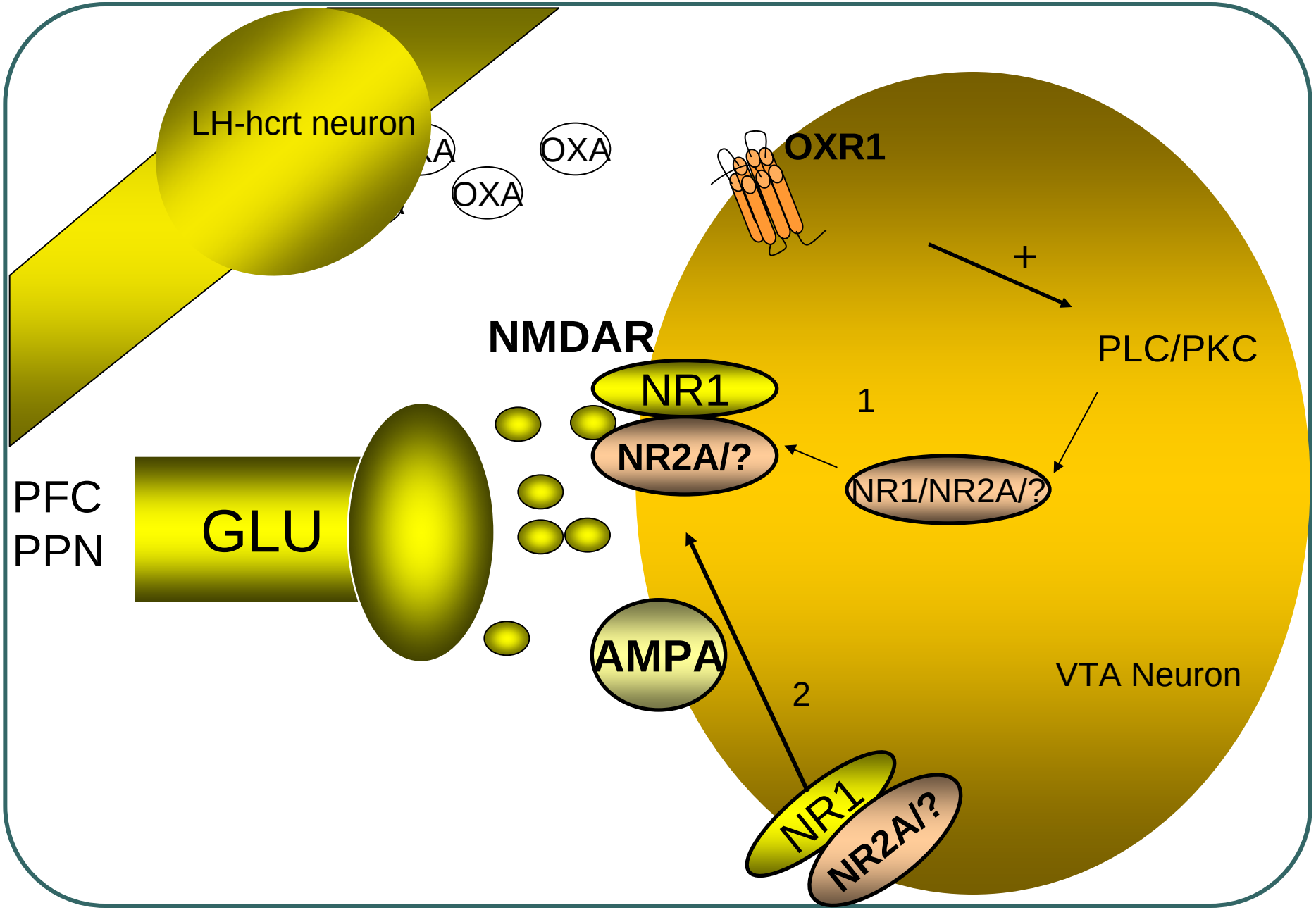
Orexin/Hypocretin Pharmacology



OxA/Hcrt1 mediated potentiation of NMDAR EPSCs is inhibited by OX1/hcrt1 receptor antagonist



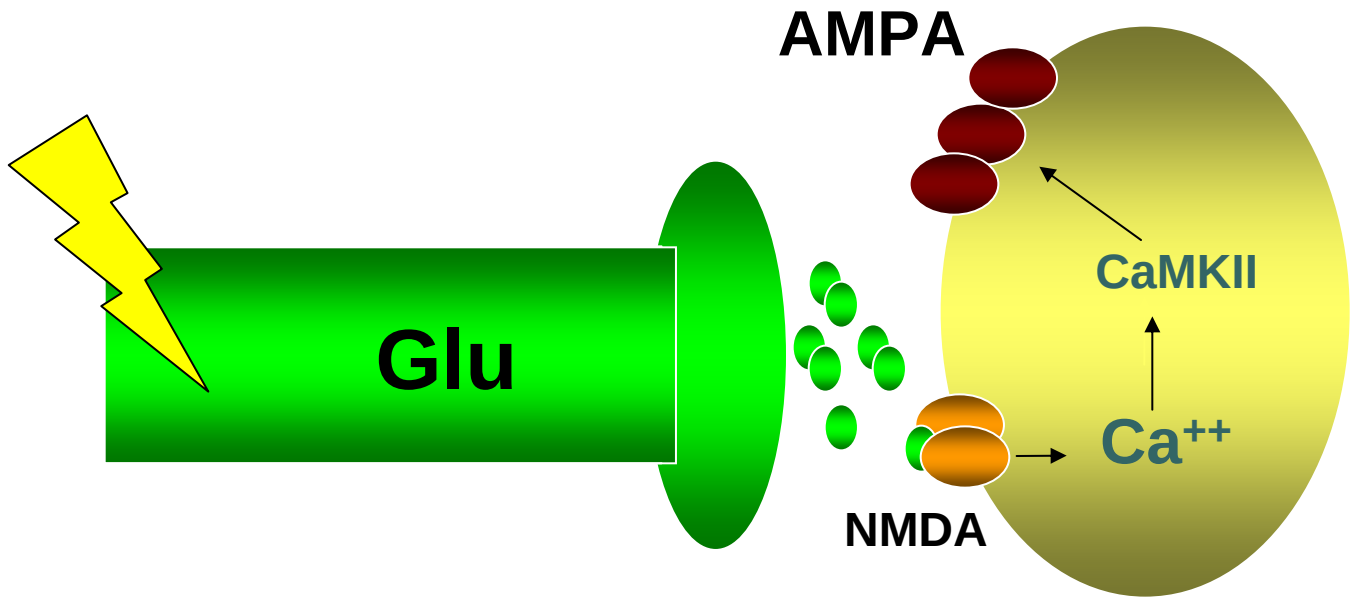
n=8


LH-hcrt neuron
OXA
OXA
OXR1
+
PLC/PKC
NMDAR
NR1
NR2A/?
1
NR1/NR2A/?
PFC
PPN
GLU
AMPA
2
VTA Neuron
NR1
NR2A/?

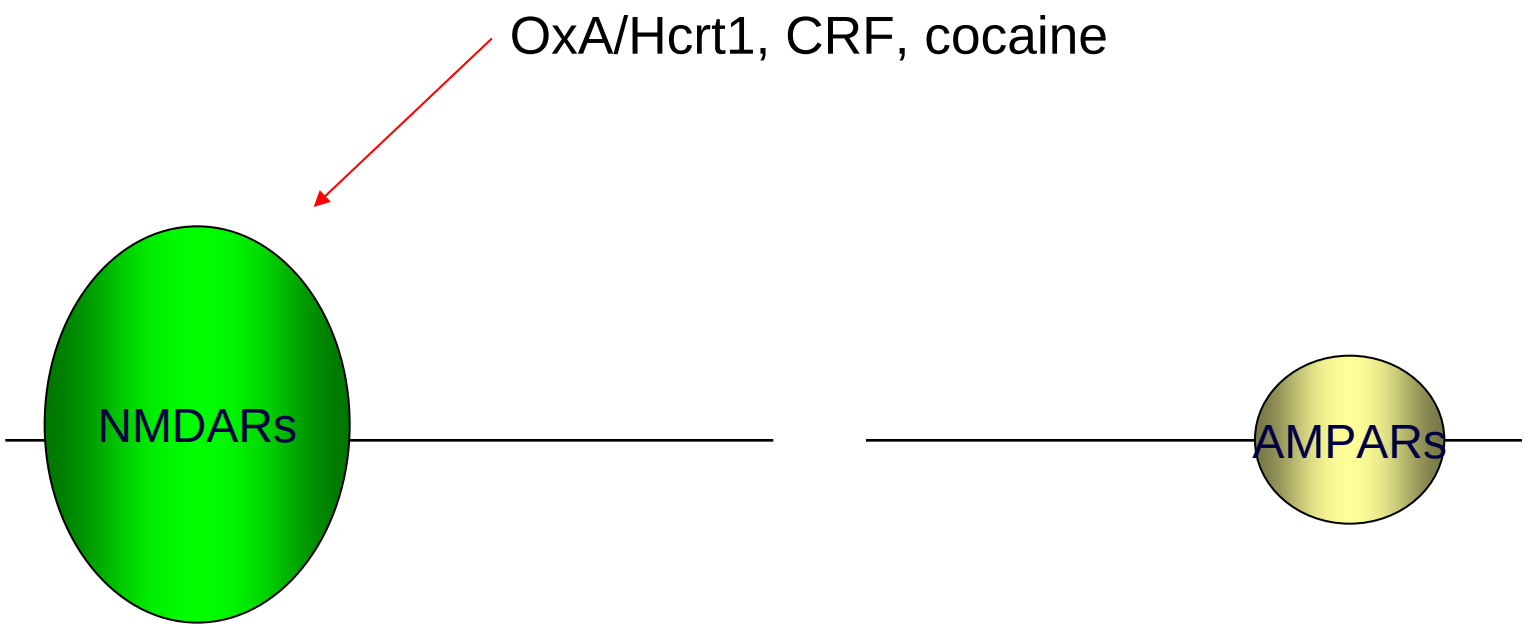
OxA/Hcrt1 on AMPAR synaptic transmission

- Activation of NMDARs is an important component for VTA long term potentiation (LTP)

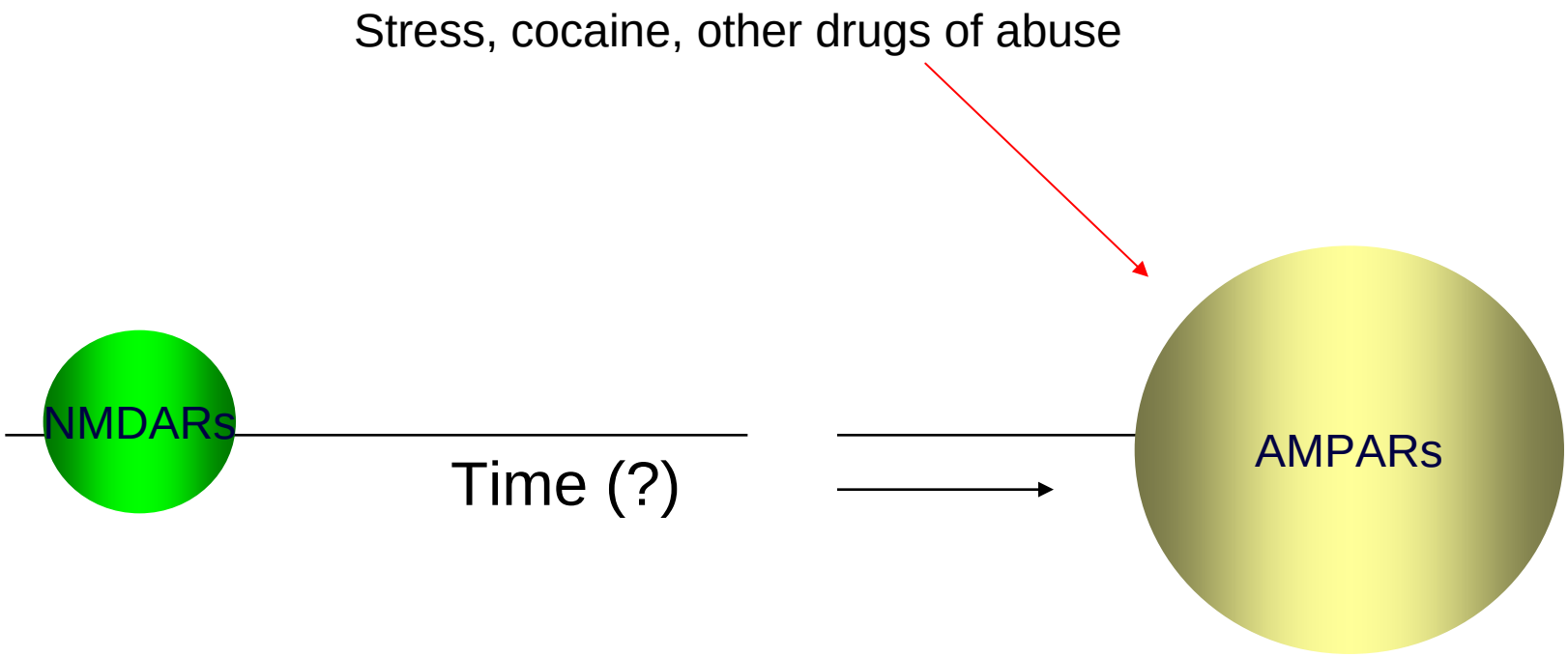
- AMPAR/NMDAR is measure of LTP



NMDAR activation precedes AMPAR plasticity

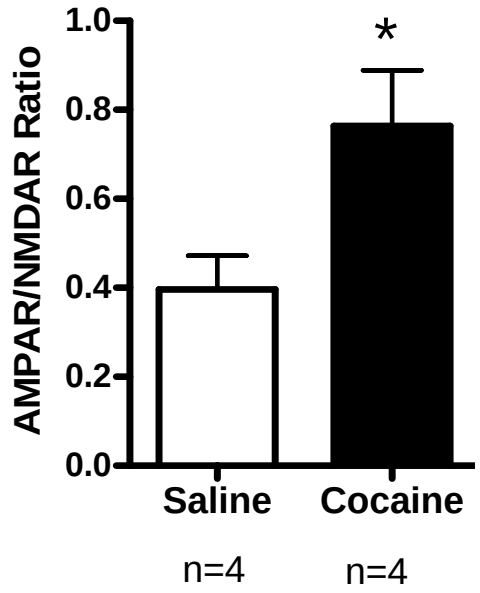


NMDAR activation precedes AMPAR plasticity



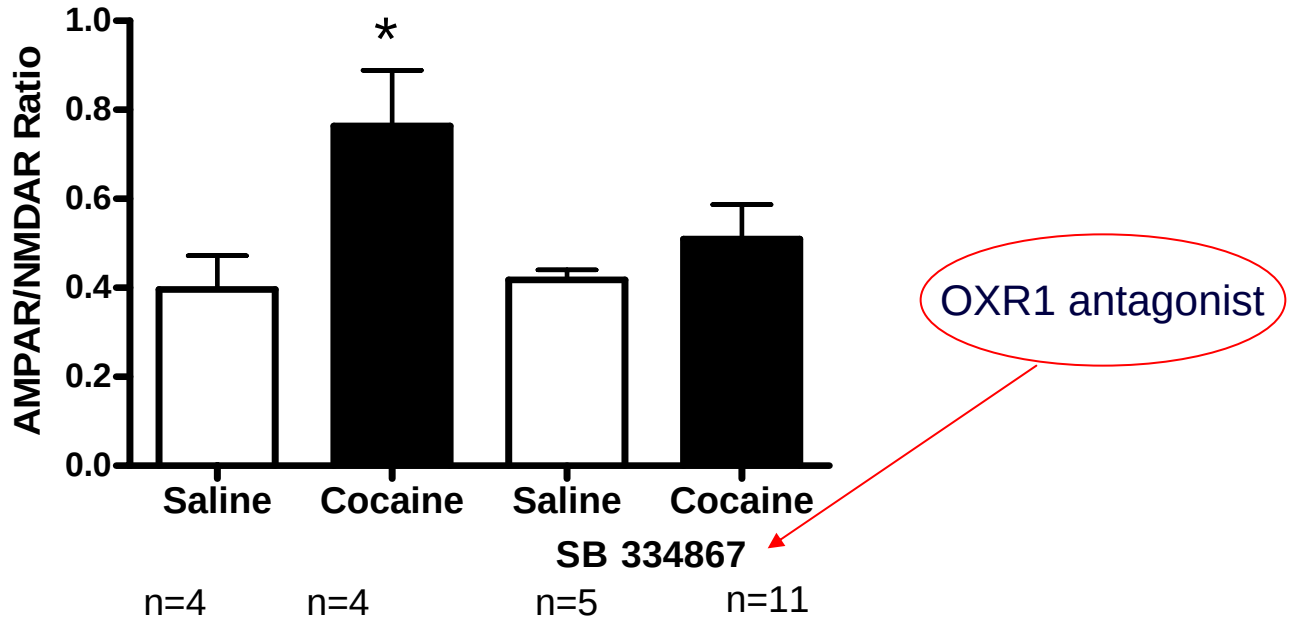
Does orexin A potentiation of NMDARs facilitate cocaine-mediated AMPAR plasticity?

OXR1/Hcrt1R antagonist blocks cocaine induced potentiation of AMPAR/NMDAR ratio



5 days cocaine or saline +/- OXR1 antagonist

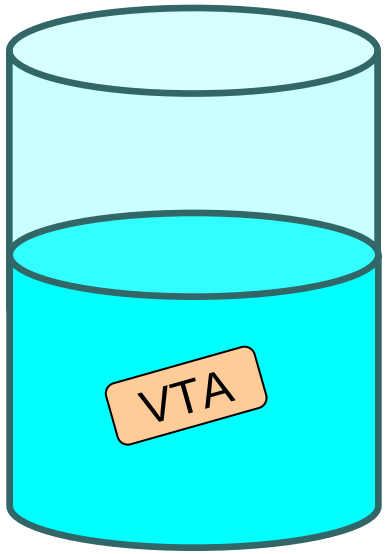
OXR1/Hcrt1R antagonist blocks cocaine induced potentiation of AMPAR/NMDAR ratio

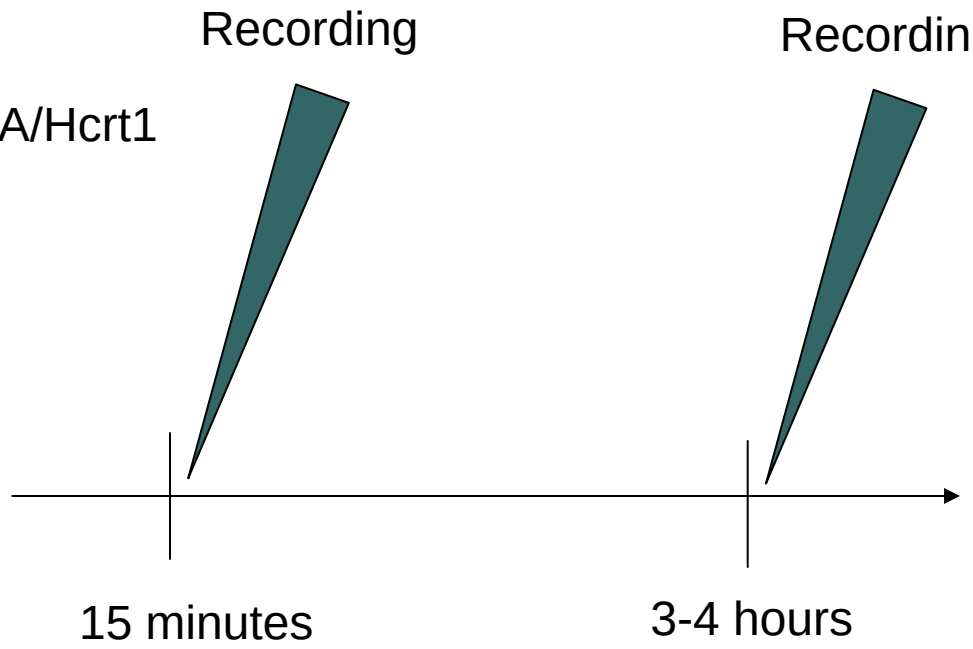


5 days cocaine or saline +/- OXR1 antagonist

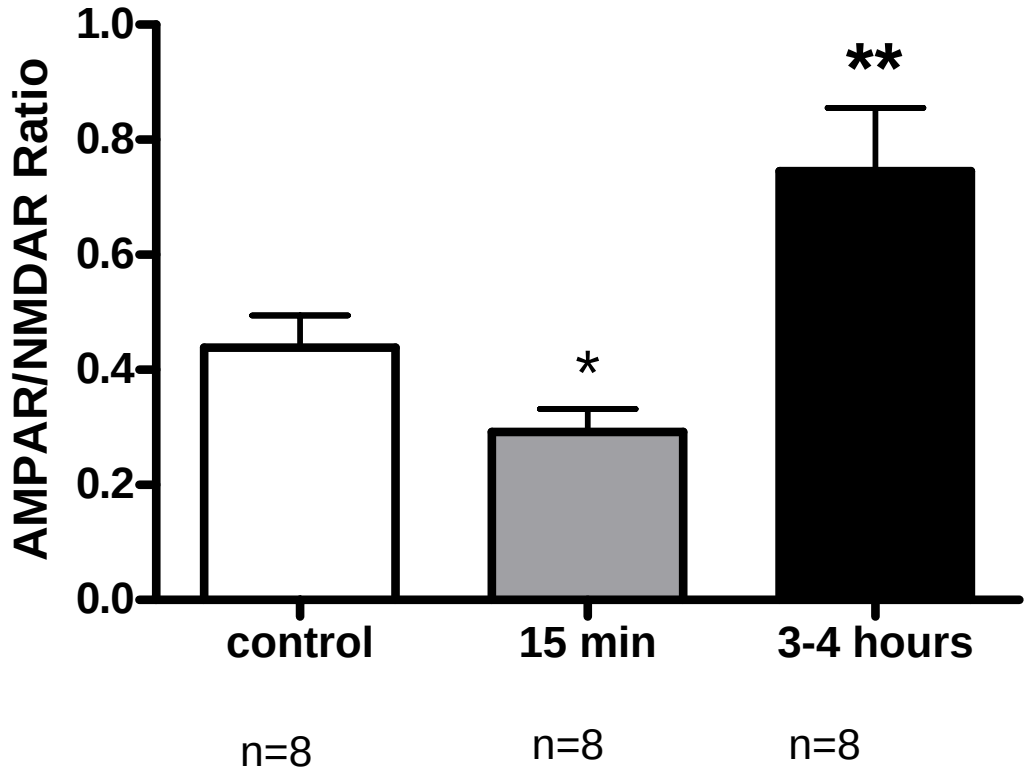
Does OxA/Hcrt1 increase AMPA/NMDA ratio?

Slices are incubated with OxA/Hcrt1 for 5 minutes

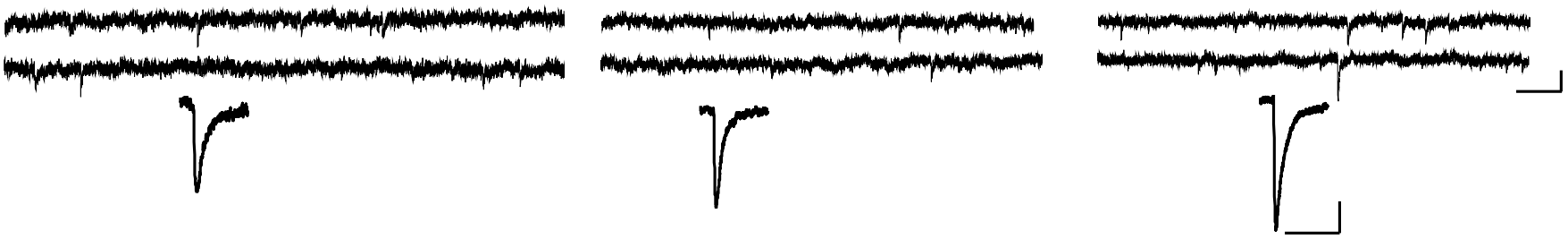


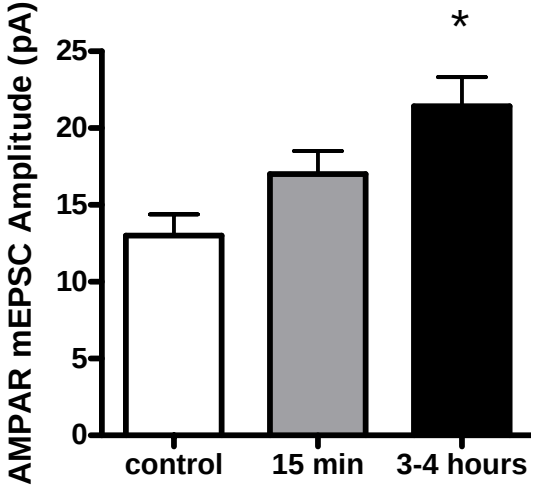


OxA/Hcrt1 increases AMPAR/NMDAR hours after application



OxA/Hcrt1 causes a late phase increase in AMPAR mediated synaptic transmission





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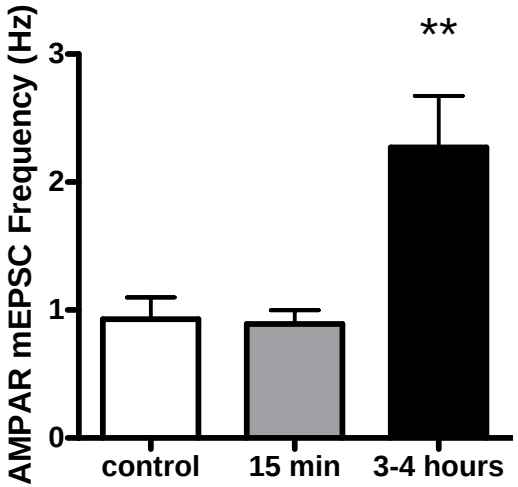
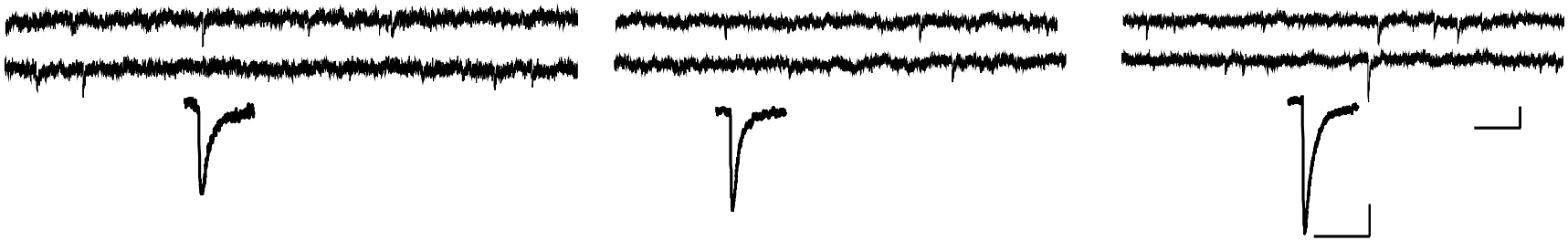
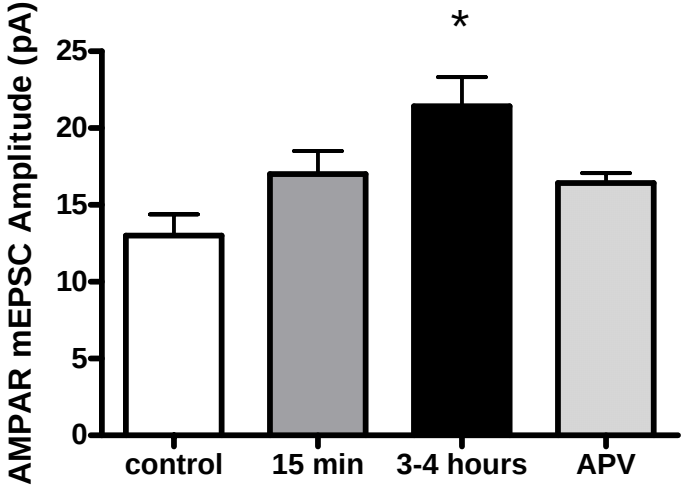
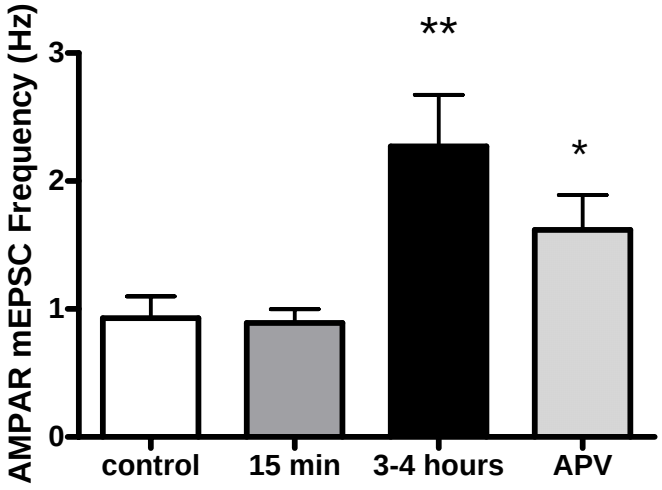


OxA/Hcrt1 causes a late phase increase in AMPAR mediated synaptic transmission that is NMDAR dependent





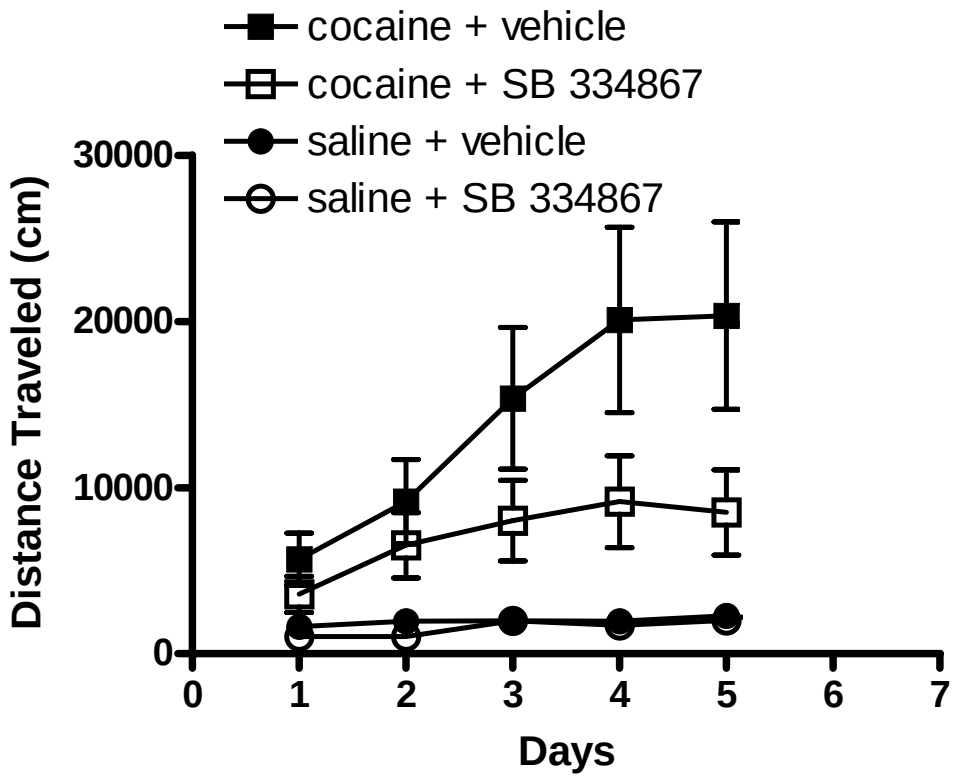


(7) (6) (7) (7)

Does OxA/Hcrt1 mediated plasticity of dopamine neurons have behavioral consequences?

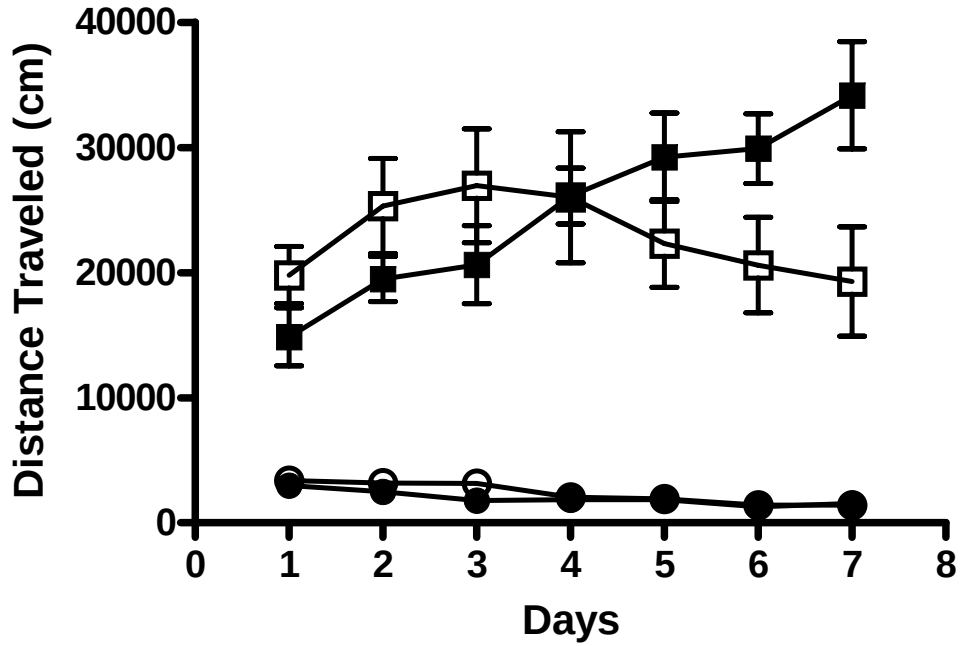
- Activation of NMDARs is an important component for VTA LTP (Bonci & Malenka, 1999) and the development of cocaine sensitization (Kalivas & Alesdatter, 1993)
- Behavioral sensitization is a progressive increase in locomotor response to the same cocaine dose.
- Since cocaine sensitization is dependent on NMDAR activation in the VTA, we hypothesized that OxA/Hcrt1 may have a role in behavioral sensitization to cocaine.

OXR1/Hcrt1R antagonist blocks cocaine sensitization



n=13

Behavioral sensitization is blocked with intra-VTA injections of OXR1/Hcrt1R antagonist



Cocaine (ip)

- Intra-VTA vehicle (12)
- Intra-VTA SB334867 (12)

Saline (ip)

- Intra-VTA vehicle (8)
- Intra-VTA SB334867 (10)

Hypothesis

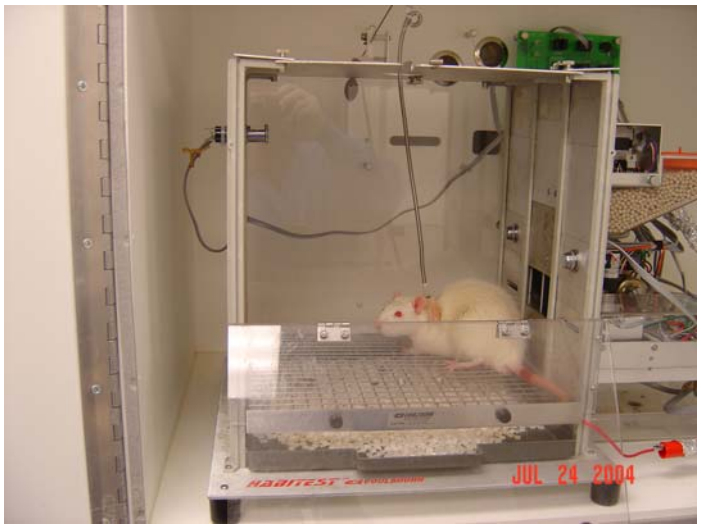
Orexin/hypocretin has a profound role in altering synaptic plasticity in a neural circuit important for motivation

↓

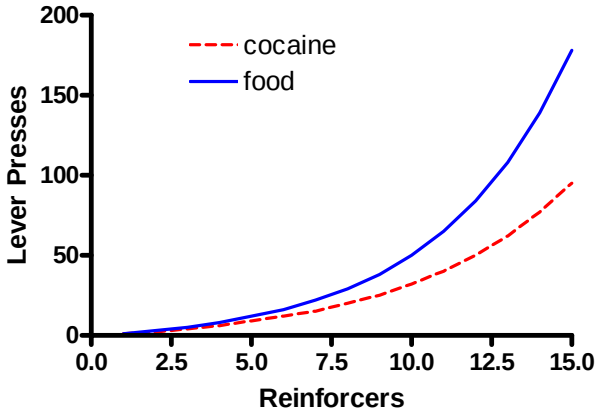
Does orexin/hypocretin signaling mediate motivated behavior?

ie. if orexin/hypocretin receptors are blocked, will rats work as much to get cocaine?

Self-administration Progressive Ratio



0.5 mg/infusion cocaine
Paired with tone and light

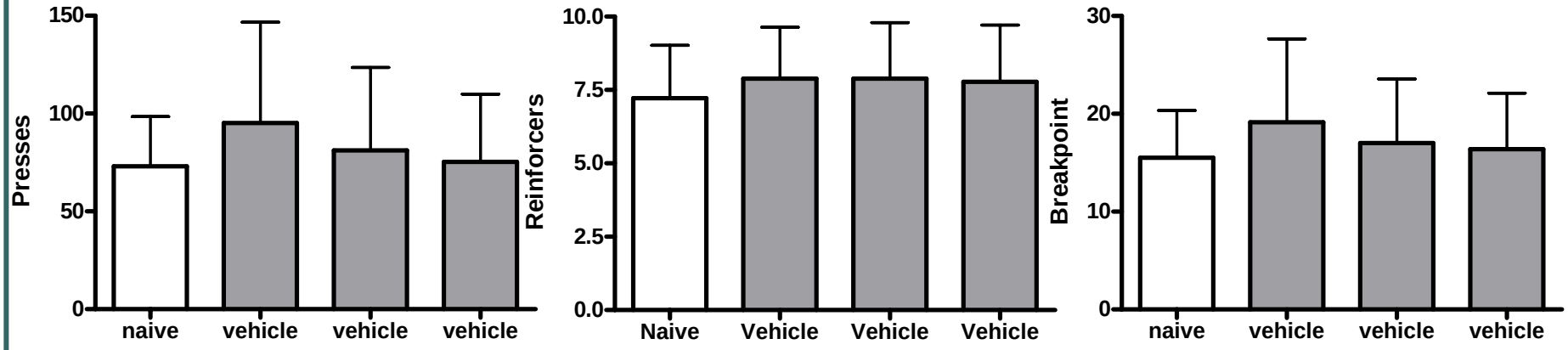


Progressive ratio

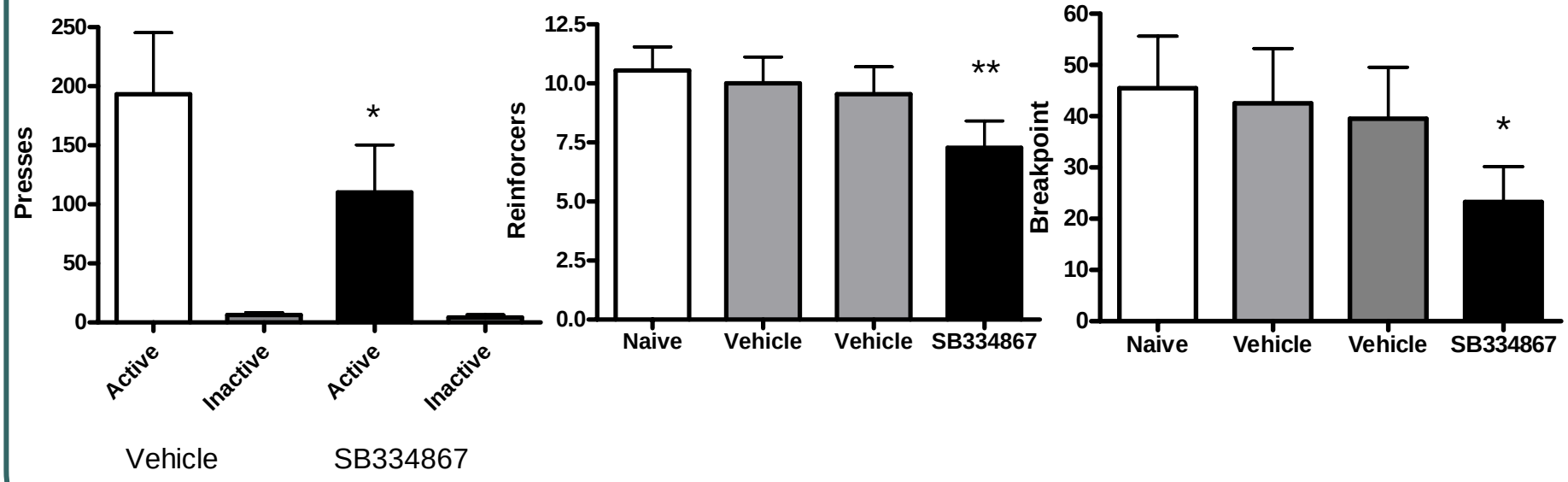
Surgery → FR1 → FR3 → FR5 → 1 2 3 4

Naive
Vehicle
Vehicle
SB 334867

Vehicle treated rats do not reduce pressing for the duration of the experiment



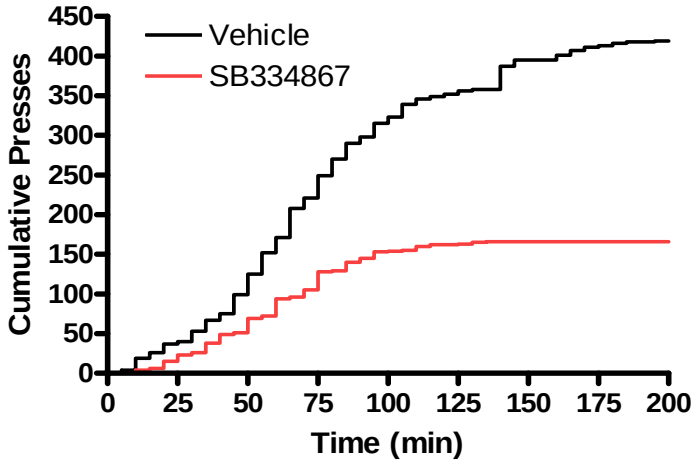
OXR1/Hcrt1 antagonist reduces “motivation” in progressive ratio test in cocaine self-administering rats

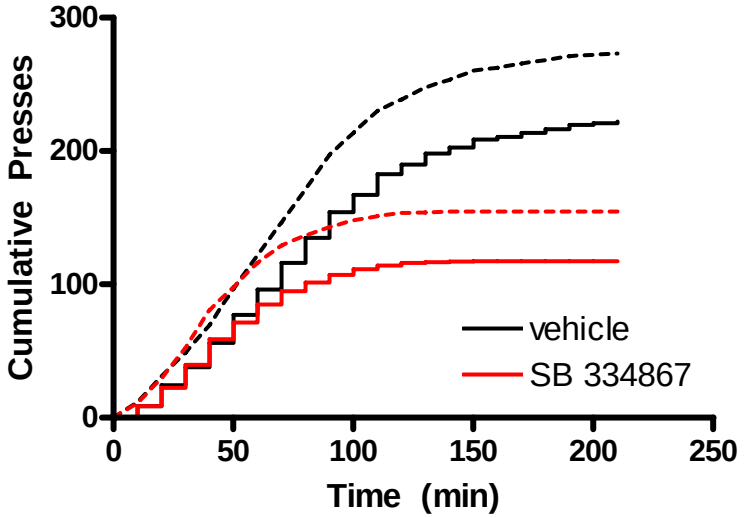


SB 334867 10 mg/kg

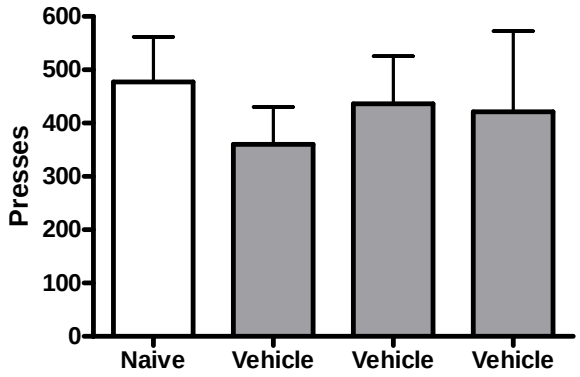
n=12

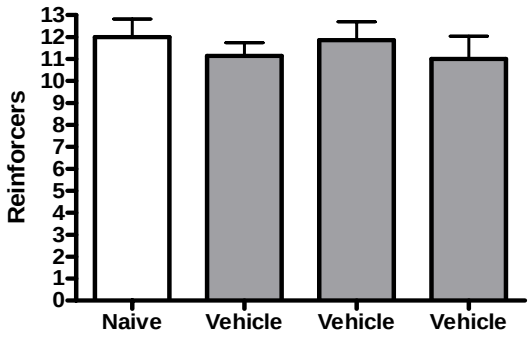
Cumulative response shows the pattern of presses for cocaine in vehicle and SB334867 treated rats

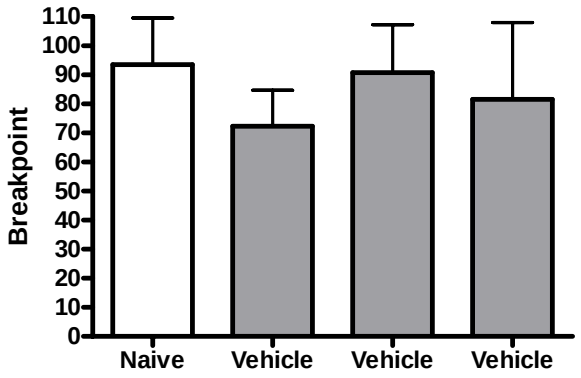




Food self administration

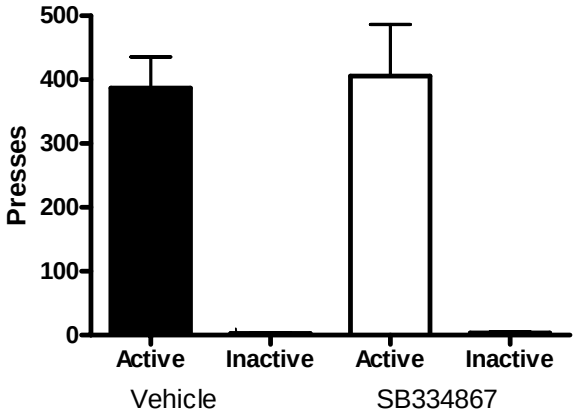


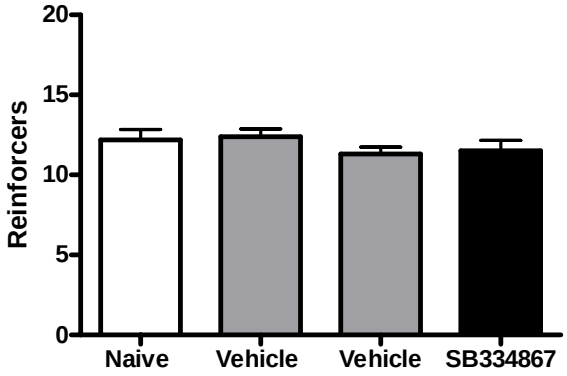


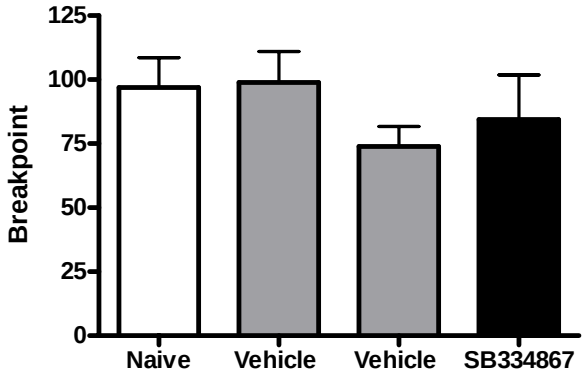


n=9

Orexin/Hcrt 1 receptor signaling is not involved in motivation for food







SB 334867 10 mg/kg

n=10

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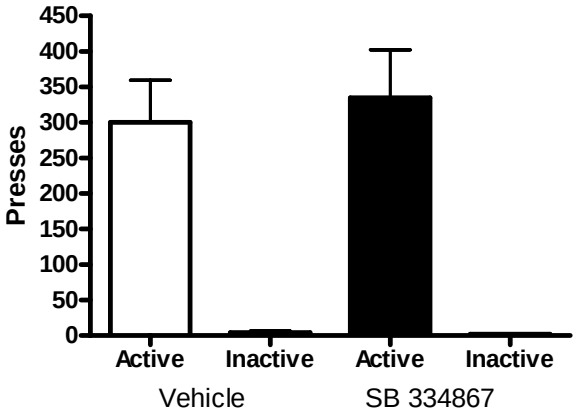
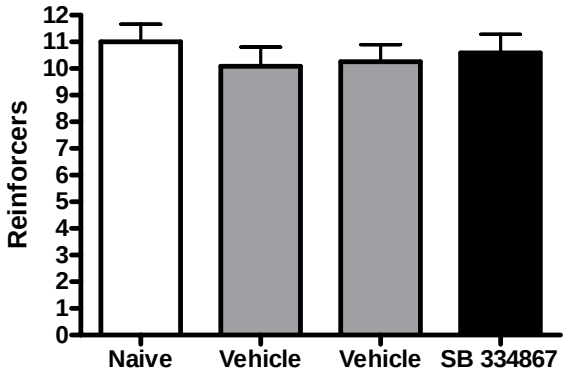
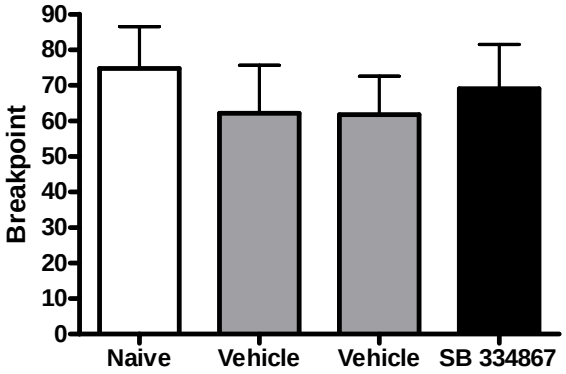


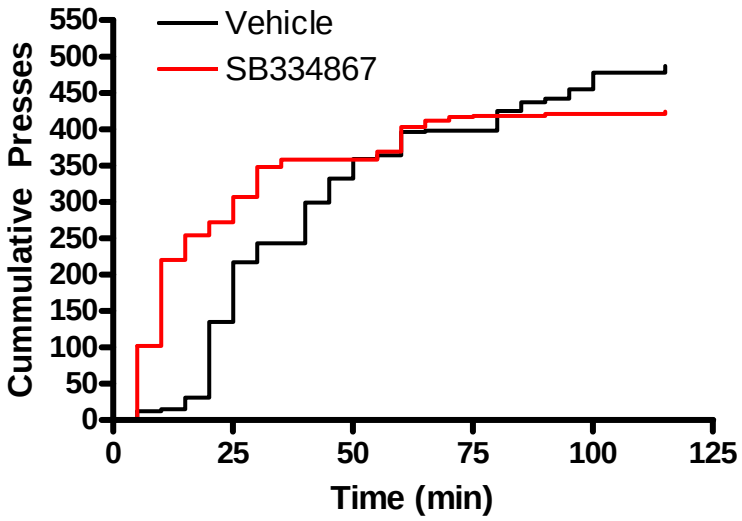


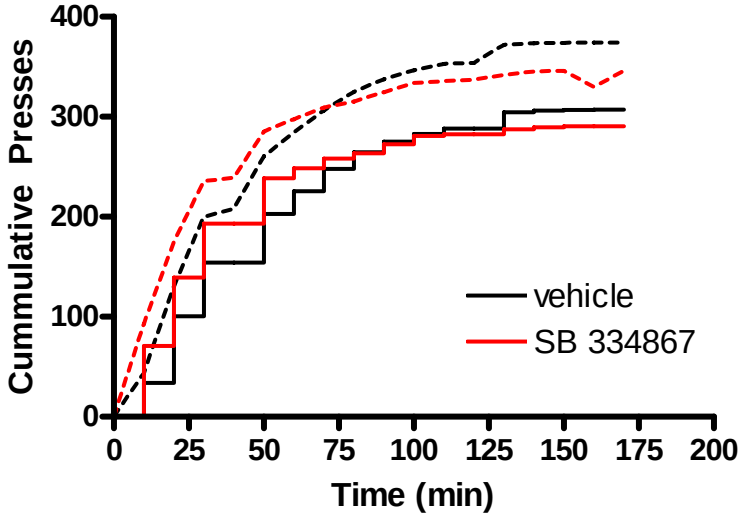


SB 334867 20 mg/kg

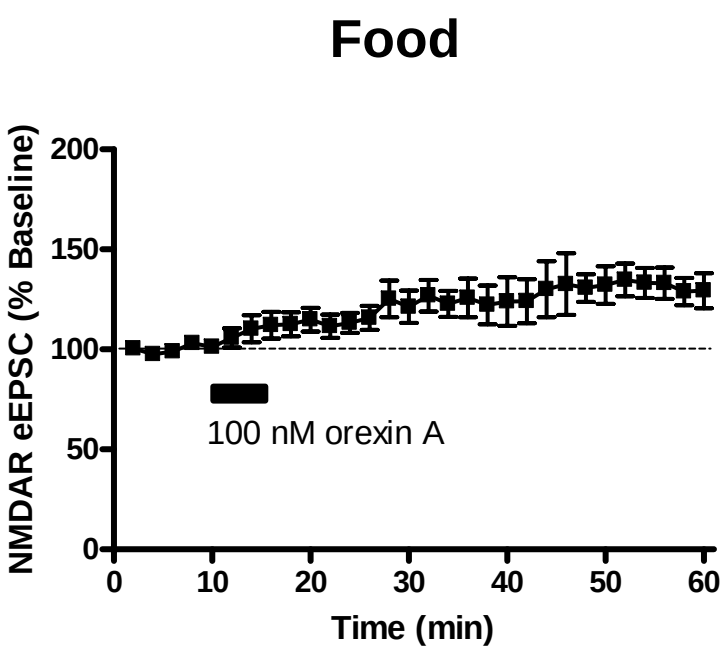
n=12

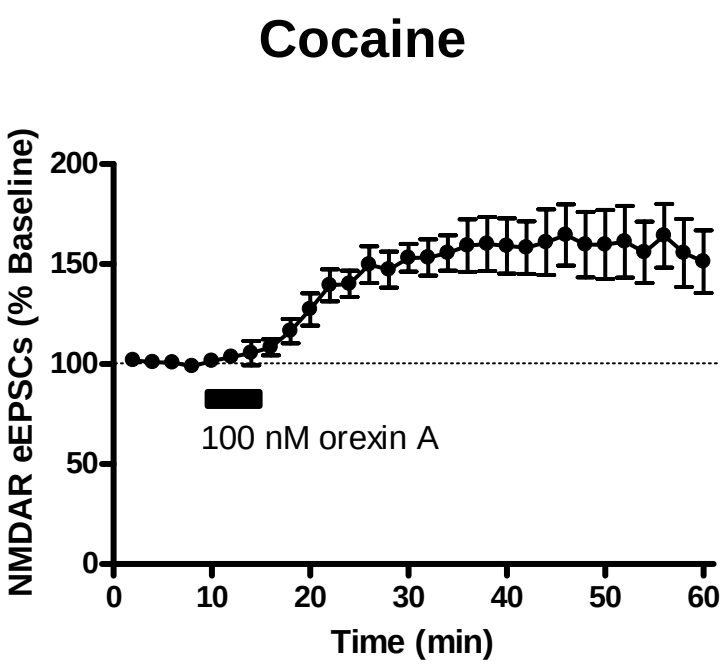
Cumulative response shows the pattern of presses for food in vehicle and SB334867 treated rats





Cocaine Self-Administration increases OxA/Hcrt1 potentiation of NMDARs

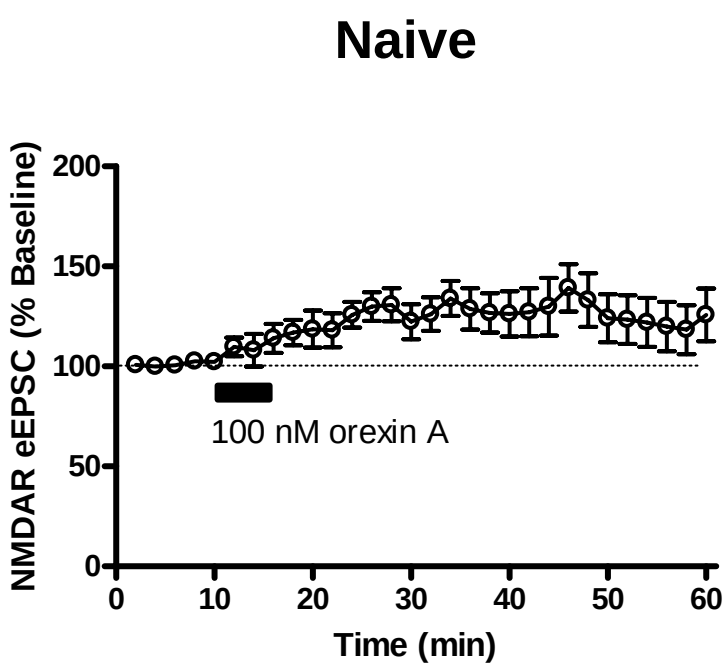


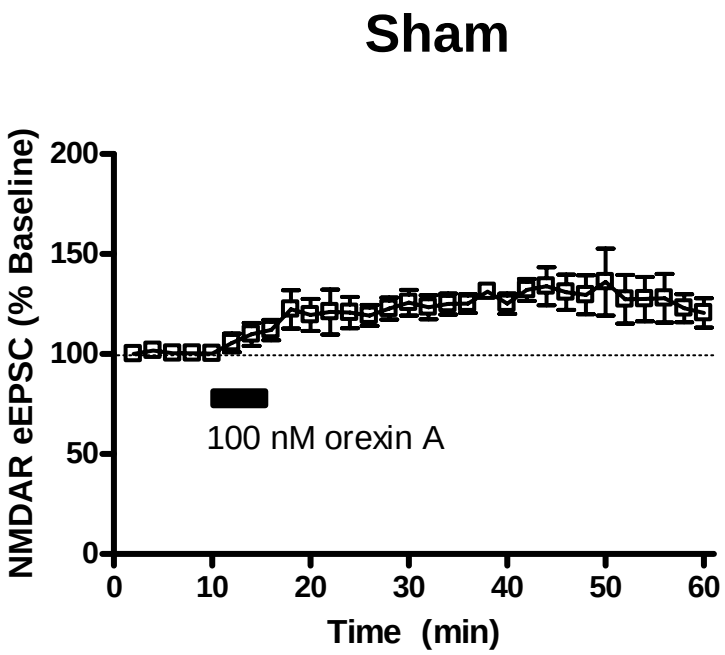


n=8

n=8

OxA/Hcrt 1 mediated potentiation of NMDAR is not different between food restricted (sham) and naïve rats

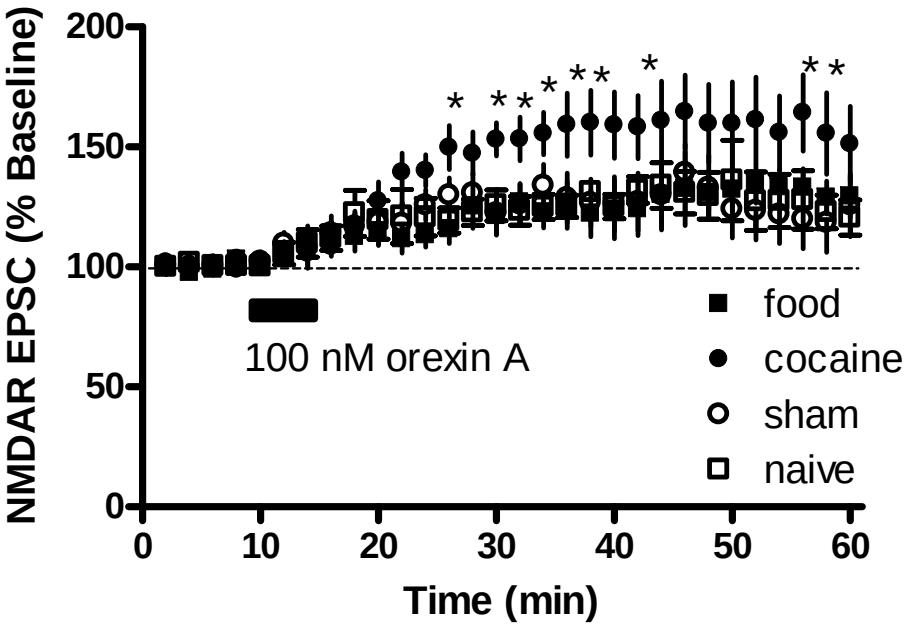


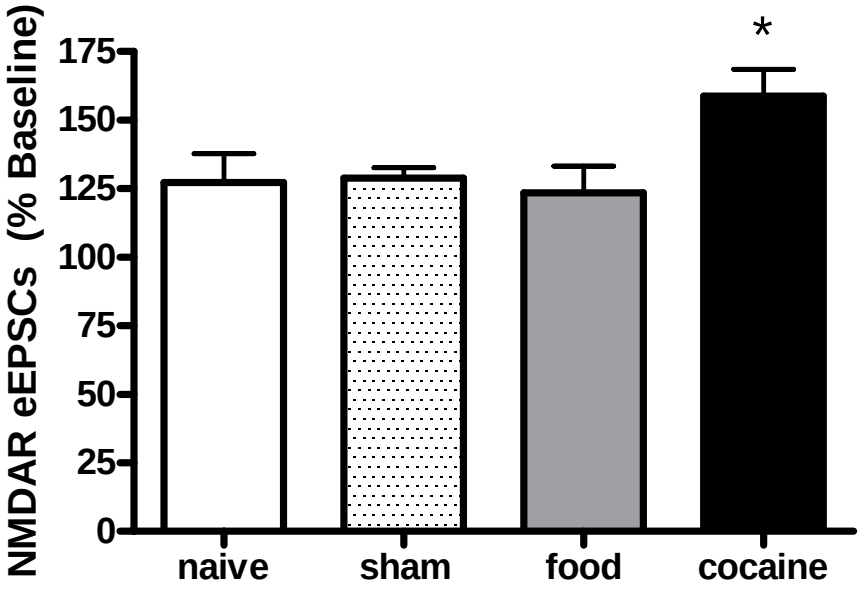


n=7

n=9

Cocaine self-administration potentiates OxA/Hcrt1-mediated synaptic plasticity in the VTA





Summary

- OxA/Hcrt1 potentiates NMDA currents in DA neurons of the VTA.

  OxA/Hcrt1 enhance:

  - synaptic strength in the mesolimbic system
  - burst firing of DA neurons, and increase in DA release.

- OxA/Hcrt1 causes a late phase increase in AMPAR mediated synaptic transmission
  - Facilitating dopamine's role in reinforcement?

Summary -2

- OXR1/Hcrt1R antagonist blocks cocaine sensitization, indicating that activation of orexin/hypocretin 1 receptors in the VTA is required for the development of sensitization.
- Orexin/hypocretin signaling is involved in “motivation” for cocaine but not food seeking
- Cocaine self-administration potentiates orexin/hypocretin-mediated plasticity in the VTA

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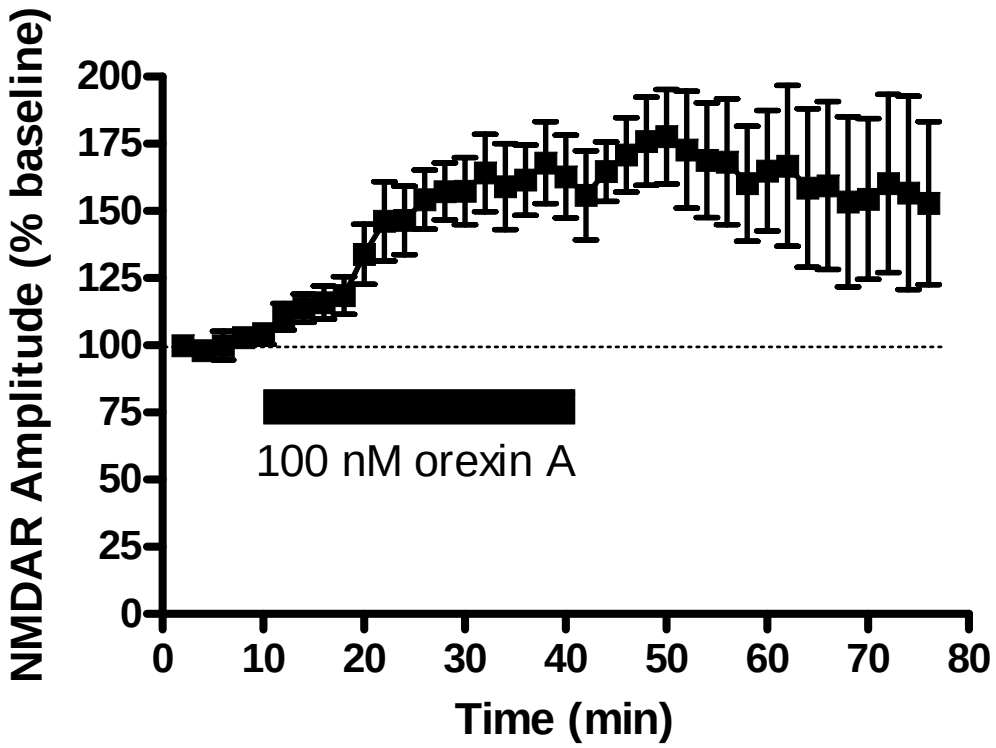
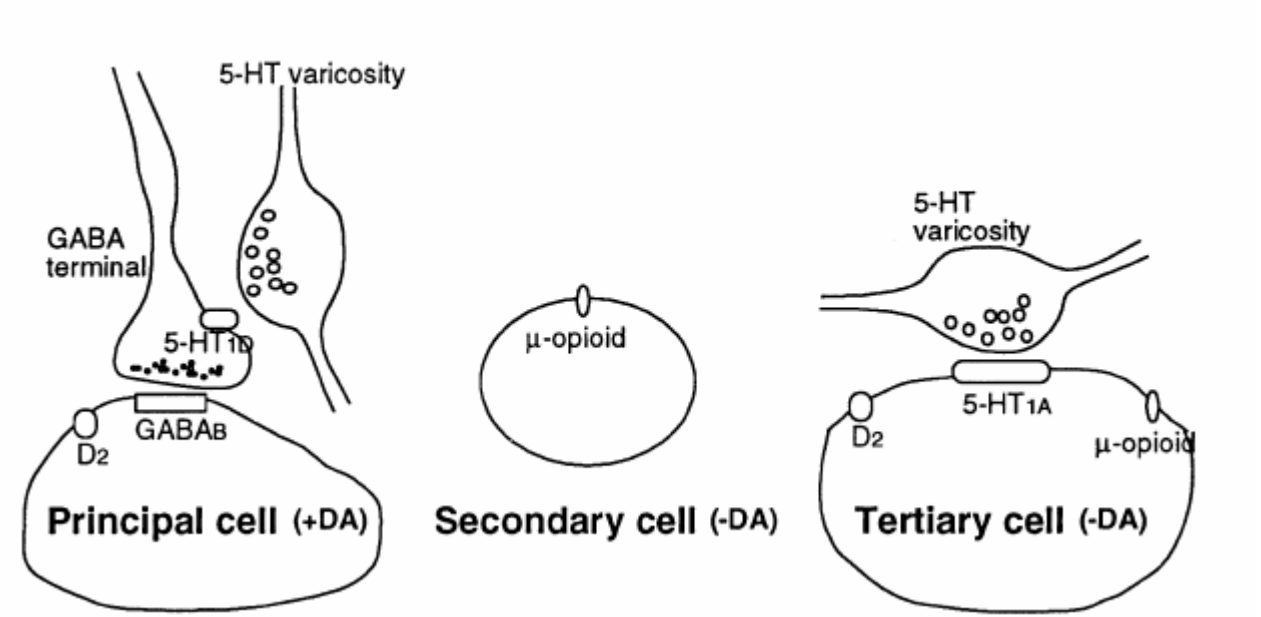
Prolonged application causes a long-lasting increase in NMDAR EPSCs



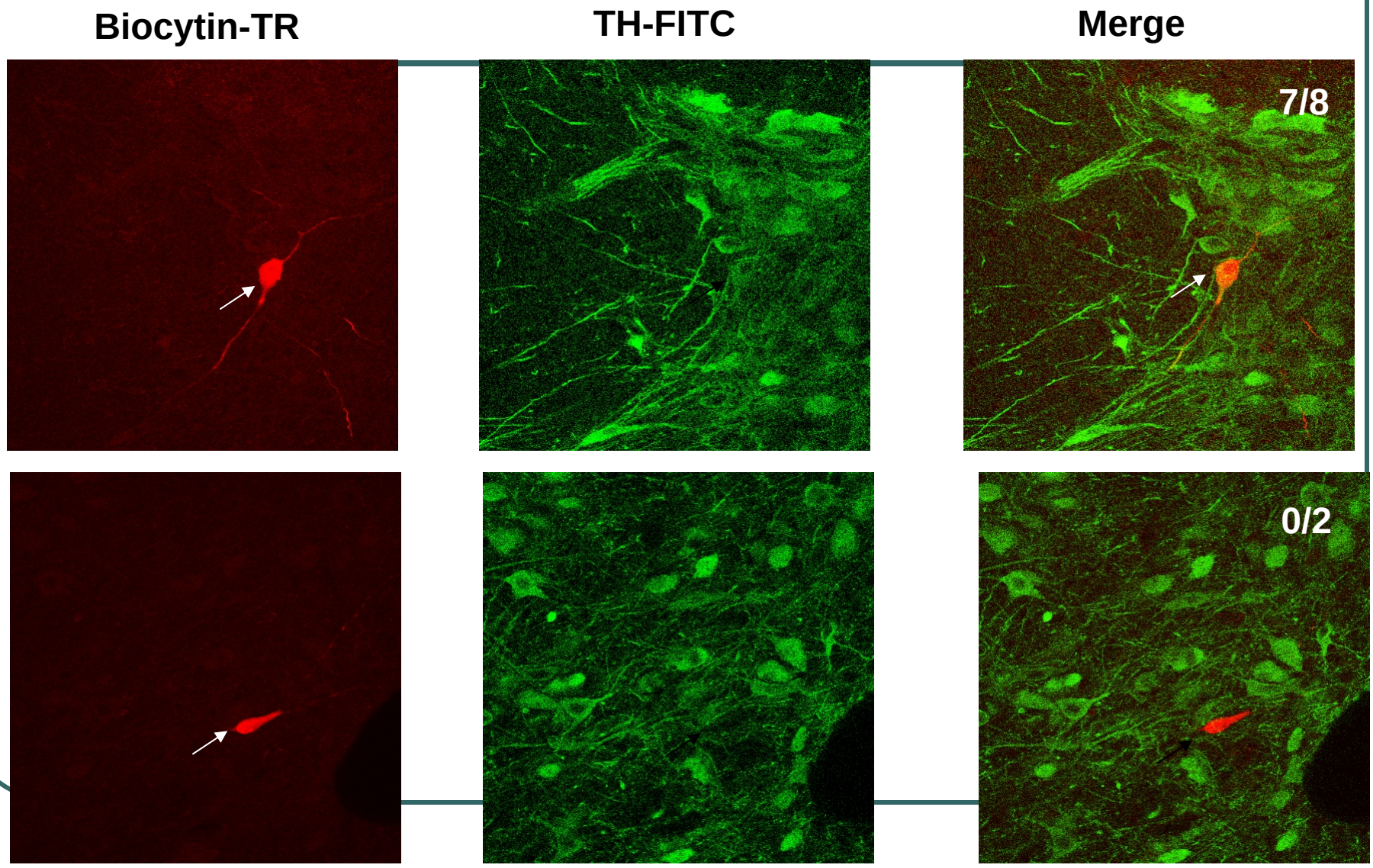
n=6

Does OxA/Hcrt1 potentiate NMDARs in dopamine neurons?

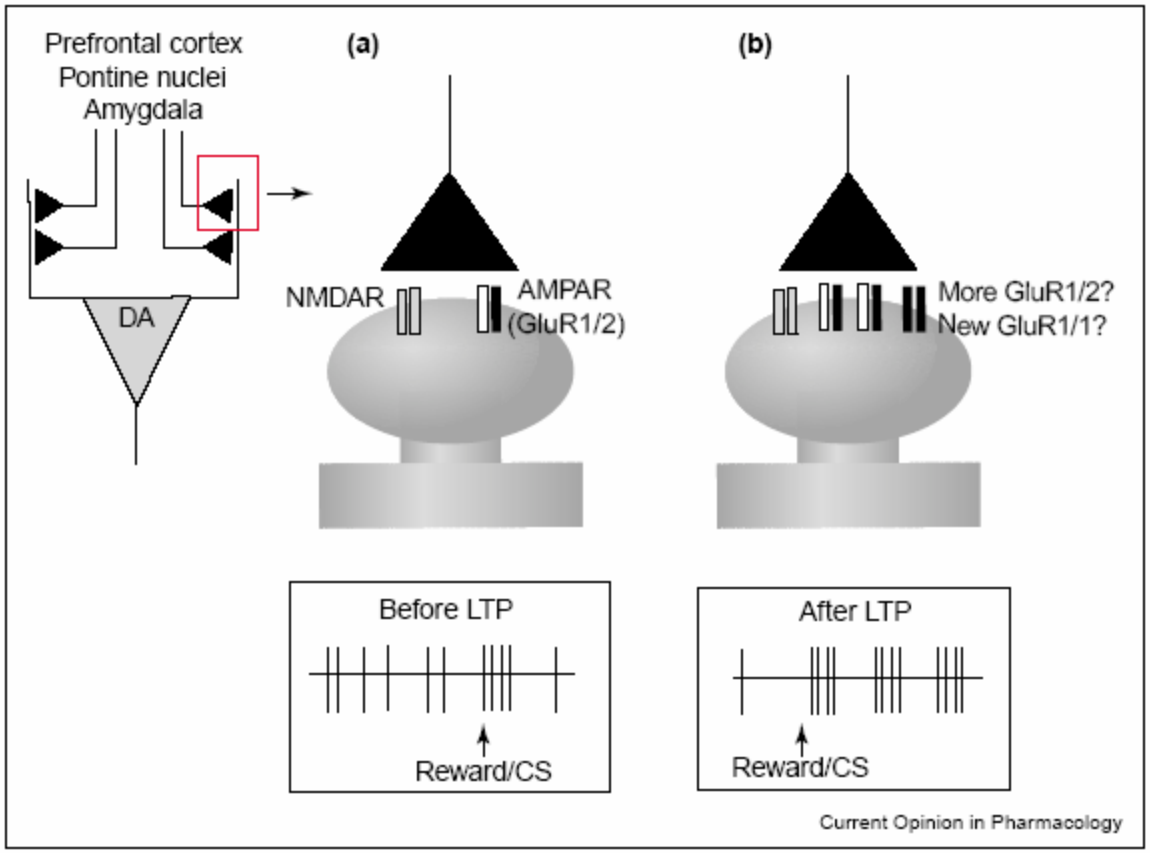


Cameron et al., 1996 Neurosci 77:

OxA/Hcrt1 increases NMDAR EPSCs in VTA dopaminergic neurons



Orexin plays a gatekeeper role in that it enables neuroplasticity in excitatory synapses in the VTA



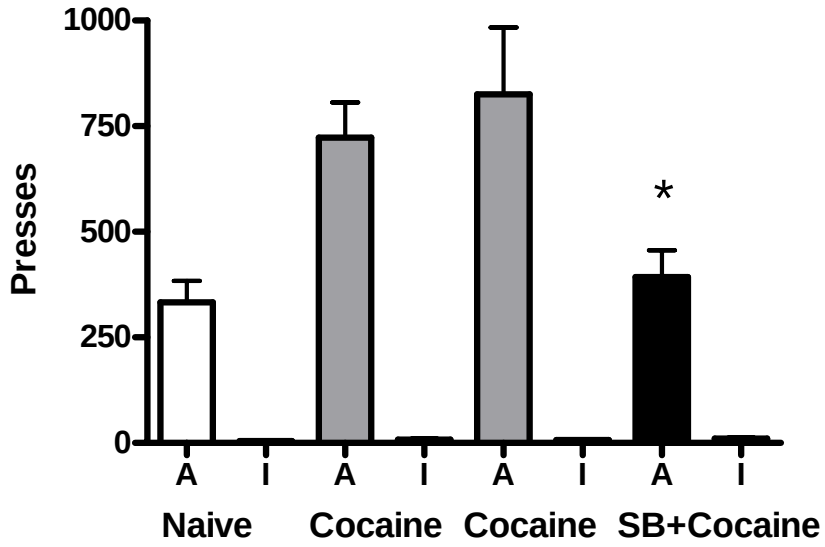
Ox/hcrt potentiation of NMDA promotes burst firing and increases DA release.

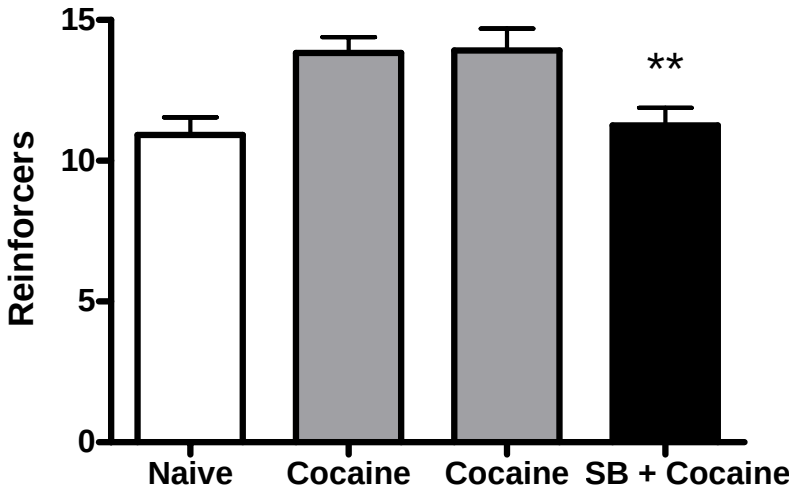
Ox/hcrt late phase potentiation of AMPARs may prolong burst firing.

This plasticity may underlie the intensification of goal-directed behavior.

Jones & Bonci 2005: 5:20-5

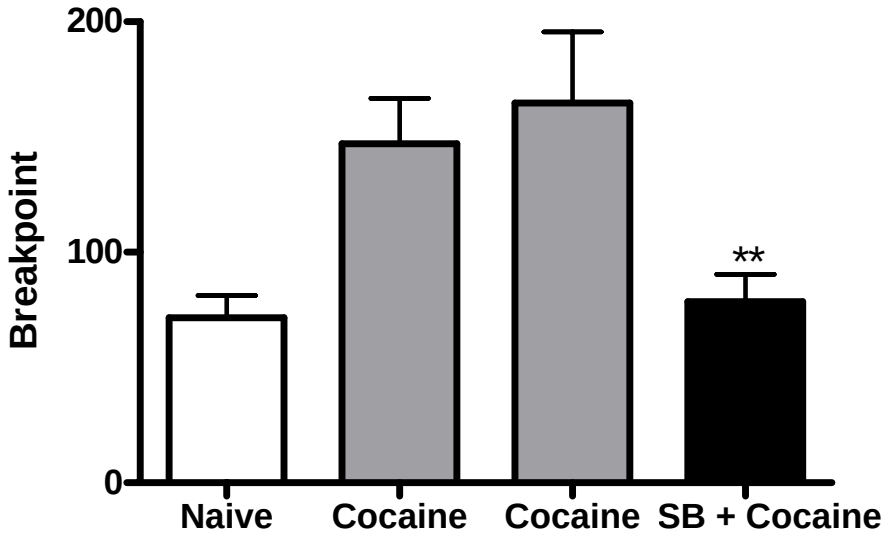
OXR1 antagonist reduces food self-administration in the presence of cocaine





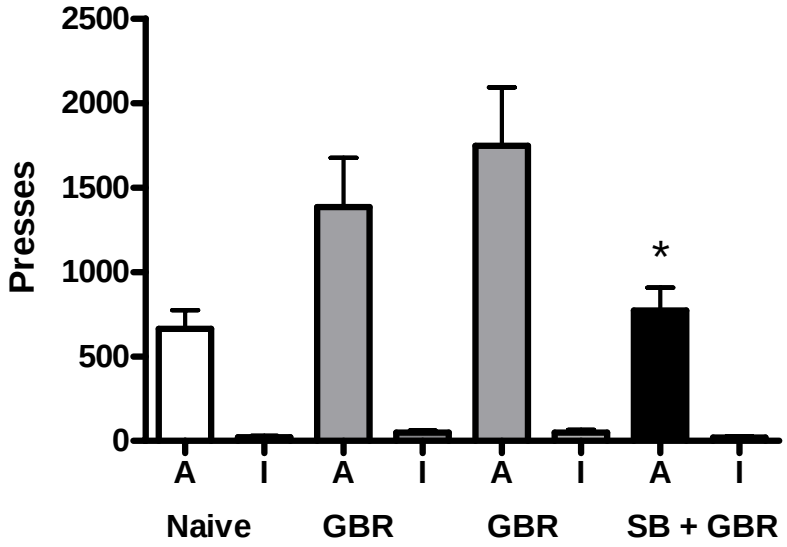
n=12

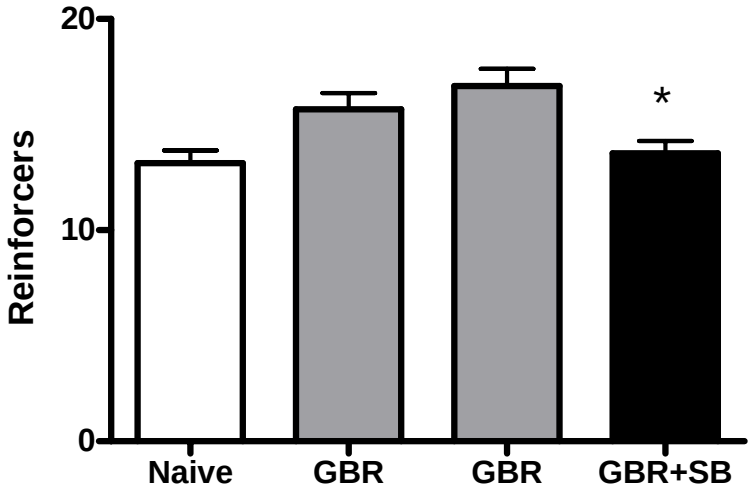
OXR1 antagonist reduces breakpoint in the presence of cocaine



n=12

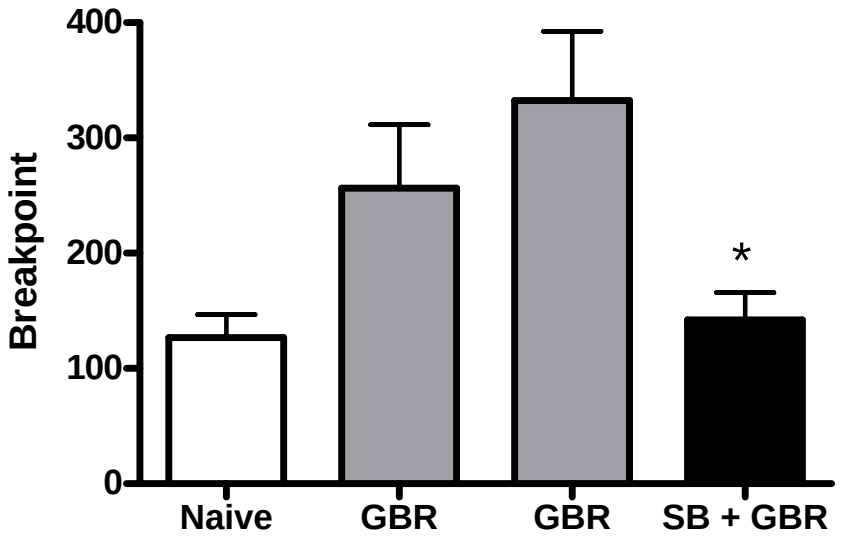
Dopamine is required for the orexin-mediated reduction in food seeking





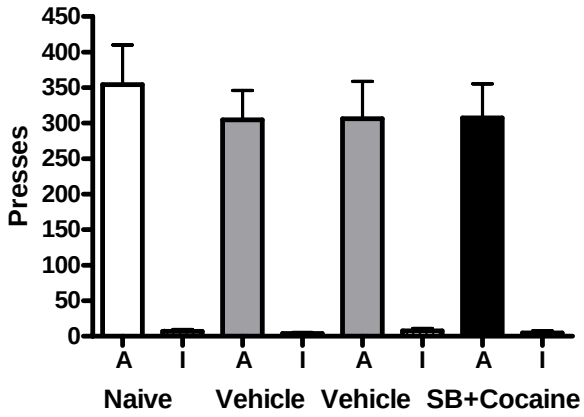
n=11

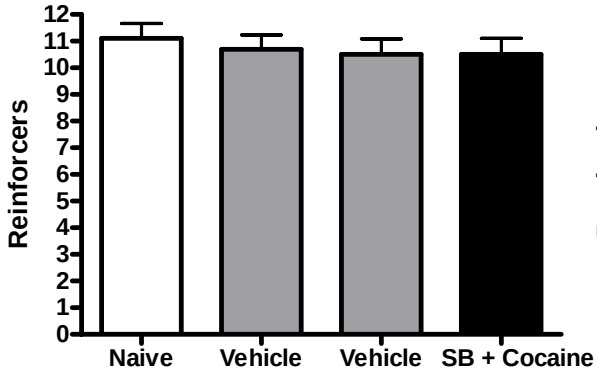
Dopamine is required for the orexin-mediated reduction in food seeking

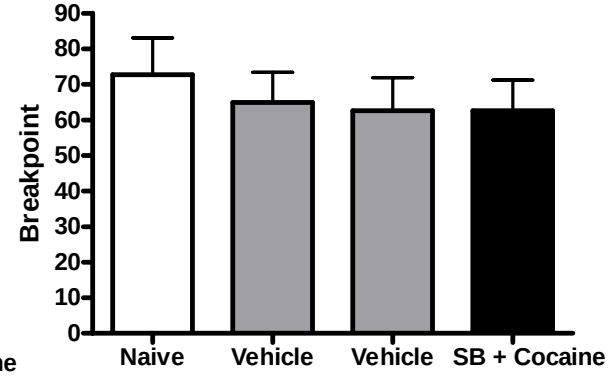


n=9

SB 334867 attenuates potentiation of breakpoint by a single injection of cocaine



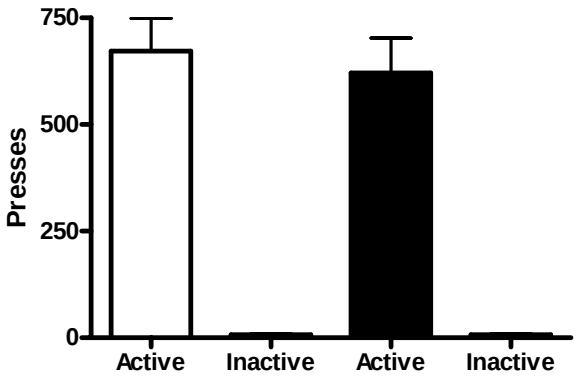


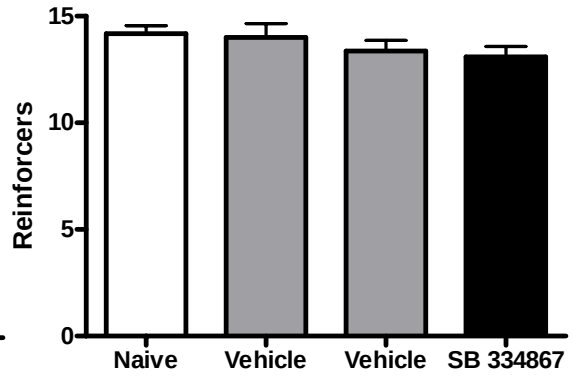


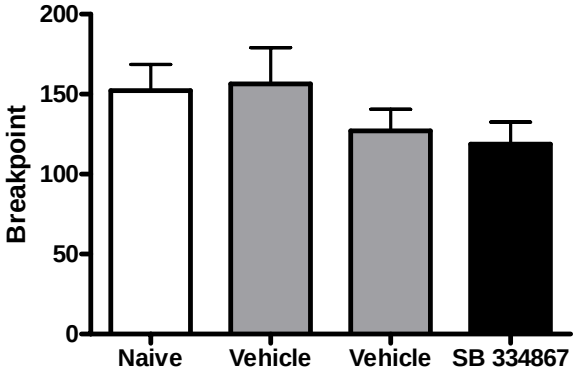
OXR1 signaling needed for cocaine PR but not food PR

- Is increased dopamine required for orexin release?
  - Can blocking orexin receptors in food treated rats reduce breakpoint after injection of GBR12909 (5 mg/kg) or cocaine (15 mg/kg)?
- Is orexin signaling involved only for highly motivational substances?
  - If you increase the reinforcing value of the reward, ie. Sucrose or high fat, will the orexin antagonist reduce seeking?
- Does cocaine potentiate orexin release/signaling?

SB 334867 (10 mg/kg) does not reduce motivation for sucrose

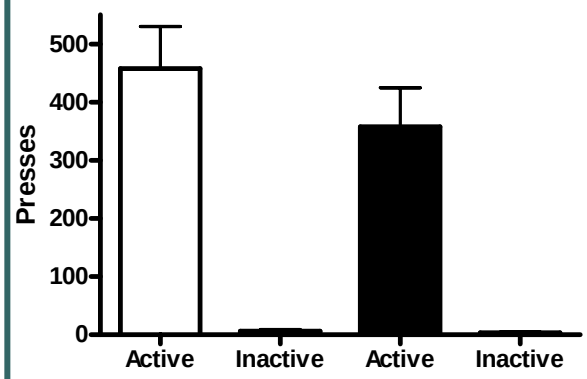


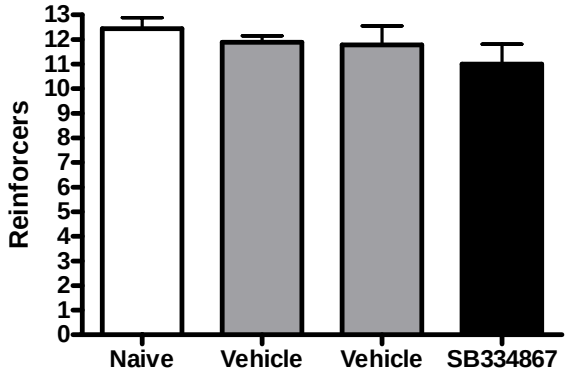


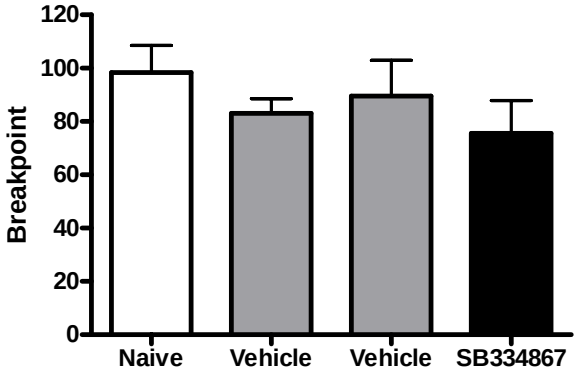


n=12

SB 334867 (20 mg/kg) does not reduce motivation for sucrose







n=9

OXR1 signaling needed for cocaine PR but not food PR

- Is increased dopamine required for orexin release?
  - Can blocking orexin receptors in food treated rats reduce breakpoint after injection of GBR12909 (5 mg/kg) or cocaine (15 mg/kg)?
- Is orexin signaling involved only for highly motivational substances?
  - If you increase the reinforcing value of the reward, ie. Sucrose or high fat, will the orexin antagonist reduce seeking?
- Does cocaine/dopamine potentiate orexin release/signaling?
  - Is there a change in pre-pro orexin in the LH?
  - Is there an alteration of orexin-mediated plasticity in the VTA?

Future experiments

- Are sucrose pellets not reinforcing enough? Is orexin signaling involved in motivation for high fat pellets?
- Does chronic cocaine change levels of pre-pro orexin or orexin A released?
- Is the OXR1 antagonist mediating the reduction in cocaine seeking acting in the VTA?

Orexin and Self-Administration

- Single injection (icv) of OxA induced persistent elevations of ICSS thresholds in drug naïve rats (Boutrel et al., 2006)
- OxA (icv) reinstated cocaine & food self admin (2 wk extinction) (Boutrel et al., 2006)
- OxA induced reinstatement was partially blocked by adrenergic and CRF antagonists (Boutrel et al., 2006)
- OXR1 antagonist (ip) blocked footshock induced reinstatement (Boutrel et al., 2006)
- OxA (icv) for 3 consecutive days did not alter cocaine self administration (Boutrel et al., SFN 2004)
- OxA (icv) did not alter progressive ratio for cocaine (0.25 mg/infusion; Boutrel et al., SFN 2004)