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Acupuncture of the Shenmen (HT-7) channel has a strong inhibitory effect on ethanol (ETOH)-induced dopamine (DA) release and prevents the reduction of dopamine (DA) by chronic ETOH (Zhao et al., 2006). GABA neurons in the ventral tegmental area (VTA) regulate DA neuron activity and release in the nucleus accumbens (NAcC). They also express mu-opioid receptors (Fig. 1) and their firing rate is inhibited by ETOH and opioids (Fig. 2).

INTRODUCTION

Acupuncture reduces ethanol inhibition of VTA GABA neuron activity and ethanol self-administration: role of endogenous opioids

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Electrophysiology: All 2-viro recordings were performed in mature (30±50 g) male Wistar rats. VTA GABA neurons were recorded (filtered at 1-3 kHz, 2000X) with 3M KCl-filled micropipettes under isoflurane anesthesia in a stereotactic apparatus on an anterolateral table and characterized according to spiking characteristics and response to anterolateral input (Steffensen et al., 1998, Stobbs et al., 2004, Allison et al., 2006, Lassen et al., 2007).

METHODS

ELECTROPHYSIOLOGY: At 2 viro recordings were performed in mature (30±50 g) male Wistar rats. VTA GABA neurons were recorded (filtered at 1-3 kHz, 2000X) with 3M KCl-filled micropipettes under isoflurane anesthesia in a stereotactic apparatus on an anterolateral table and characterized according to spiking characteristics and response to anterolateral input (Steffensen et al., 1998, Stobbs et al., 2004, Allison et al., 2006, Lassen et al., 2007).

Figure 1: μ-Opioid receptors are localized to VTA GABA neurons. The electron micrograph shows a longitudinally-cut dendrite containing peroxidase reaction product to neurobiotin, indicative of a physiologically-characterized neuron. The neurobiotin-dendrite contains immunoperoxidase particles for ω(OR) (circles) that are localized to intracellular organelles. Two unlabeled terminals (UT) form a quasicontact synapse with the result that the budding dendrite is unable to communicate with the dually-labeled dendrite. In addition, unlabeled dendrite (UD) forms a tight junction with the neurobiotin/ω-OR dendrite (arrow). Scale bar, 1 μm.

Figure 2: Opioid inhibition of the VTA GABA neuron firing rate. (A) Systemic heroin (5 μg/kg) produced a moderate and prolonged inhibition of VTA GABA neuron firing rate and naloxone blocked the inhibition. The arrow indicates the time when the drug was injected. (B) Local DAMGO (10 nM; right) produced a moderate inhibition of VTA GABA neuron firing rate. Horizontal bars indicate time and length of duration of the drug injection before the bar.

Thus, we hypothesized that acupuncture, which may exert its analgesic effects through endogenous opioids, might affect the excitability of VTA GABA neurons, influence their sensitivity to ETOH (Gallegos et al., 1999; Stobbs et al., 2004; Steffensen et al., 2009; Ludlow et al., 2009) and modulate ETOH self-administration.

Figure 3: Stimulation of acupuncture sites. Acupuncture Shenmen (HT-7) points were stimulated mechanically for ETOH self-administration studies and electrically (2 Hz at threshold current for muscle twitch stimulation) for single-unit electrophysiology studies. Figures 2.3 show the locations of HT-7, PC-6 and Tail acupuncture sites.

RESULTS

Modulation of VTA GABA neuron firing rate by sensory stimulation vs acupuncture HT-7 (Shenmen) point stimulation

Figure 4: Modulation of VTA GABA neuron firing rate by stimulation of the HT-7 point vs Tail stimulation. (A) HT-7 electrical (2 Hz) at threshold current for muscle twitch stimulation produces an initial activation (EARLY) of VTA GABA neuron firing rate followed by a more prolonged inhibition (LATE). (B) Tail electrical stimulation produces only a transient increase in firing rate. (C) There was a significant difference between HT-7 and Tail LATE effects on VTA GABA neuron firing rate.

Mu-opioid receptor antagonists block the late inhibition produced by HT-7 stimulation

Figure 5: Naltrexone blocks the inhibition of VTA GABA neuron firing rate by HT-7 stimulation. (A) Intravenous administration of the mu-opioid receptor antagonist naltrexone blocks the late inhibition, but not the EARLY activation, of VTA GABA neuron firing rate. (B) Saline did not affect either the EARLY or LATE phases of HT-7 stimulation. (C) There was a significant difference between saline and naltrexone on the LATE inhibition of VTA GABA neuron firing rate.

HT-7 stimulation blocks ETOH inhibition of VTA GABA neuron firing rate

Figure 6: Comparison between HT-7 and Tail stimulation on acute ETOH (20 %) and VTA GABA neuron firing rate. (A) HT-7 stimulation blocked the transient inhibition of VTA GABA neuron firing rate by acute ETOH. (B) Saline did not affect the effects of ETOH. There was a significant difference between HT-7 and Tail stimulation on ETOH inhibition of VTA GABA neuron firing rate. (C) In addition, intravenous administration of naloxone antagonized HT-7 block of ETOH inhibition of VTA GABA firing rate.

HT-7 acupuncture reduces ETOH-reinforced behavior

Figure 7: Acupuncture at HT-7 reduces ethanol, but not food, reinforced behavior. (A) Rats manually received the stimulation of bilateral HT-7 (Shenmen, n = 6) points for 1 min immediately before testing session. Acupuncture points corresponding to bilateral tail (Tail, n = 8) and PC6 (Neiguan, n = 7) points were used as control points. Results are expressed as the mean ± S.E.M. for the amount of ethanol consumption (in g/kg) during the 30-min self-administration session. HT-7, but not Tail or PC6 stimulation significantly reduced ethanol intake (g/kg) during the 30-min session (NS = 0.05, HT-7 group vs PC6 group). B) To control for the possibility that acupuncture affects general suppression of food-pallet self-administration was performed using ethanol-naïve rats (n = 8). HT7 acupuncture did not alter food-reinforced responding.

Role for endogenous opioids in mediating HT-7 acupuncture effects on ETOH self-administration

Figure 8: Naltrexone, but not naloxone, blocks ethanol inhibition of VTA GABA neuron firing rate. (A) This ratemeter record shows a representative VTA GABA neuron with a baseline firing rate of approximately 37 Hz in the presence of 1.0 g/kg naloxone. Intraperitoneal administration of 1.0 g/kg ethanol produced typical inhibition of VTA GABA neuron firing rate. (B) This ratemeter shows the firing rate of a VTA GABA neuron in a separate experiment with a baseline firing rate of 35 Hz in the presence of 10 mg/kg naltrexone, which blocked the inhibition of VTA GABA neuron firing rate by 1.0 g/kg ethanol. (C) This graph summarizes the effects of naltrexone and naloxone on ethanol effects on VTA GABA neuron firing rate. There was a significant difference in ethanol effects between naloxone vs naltrexol. (D) Significant effect p = 0.0059 between naltrexol vs naloxone effects.

SUMMARY AND CONCLUSIONS

VTA GABA neurons express mu-opioid receptors and are inhibited by opiates.

Sensory stimulation transiently activates the firing rate of VTA GABA neurons.

HT-7 (Shenmen) point, but not Tail, stimulation inhibits VTA GABA neuron firing rate with recovery in 5 min, suggesting that stimulation of this specific acupuncture point modulates the activity of midbrain GABA neurons.

HT-7 inhibition of VTA GABA neuron firing rate is blocked by naloxone, suggesting that HT-7 acupuncture modulates the activity of these neurons via endogenous opioid activation of their mu-opioid receptors.

HT-7, but not Tail or PC-6, acupuncture, reduces ETOH self-administration.

HT-7 acupuncture does not affect food reinforcement.

Morphine abolished the suppressive effect of HT-7 acupuncture on ETOH self-administration, suggesting that there is a complex interaction between endogenous opioids and ETOH for the effects of HT-7 acupuncture on reduction of ETOH self-administration.

These findings demonstrate that stimulation of specific acupuncture points modulates the activity of GABA neurons in the VTA via mu-opioid receptors and that endogenous opioid activation by acupuncture may be useful in counteracting the rewarding properties of ETOH.

Particularly, delta-opioid receptor, Naltrindole seems to block the ethanol inhibition of VTA GABA neurons firing rate.

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