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Title: Effect of hypocretin (orexin) on ventral tegmental area dopamine neurons in vivo

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Hypothalamic neurons expressing hypocretin (orexin, hcrt/orx) peptides are believed to regulate arousal and behavioral state by their projections to wake-active cell groups in the brainstem. In addition, hcrt/orx projections to the ventral tegmental area (VTA) suggest a role for the peptides in reward or goal-directed behavior. We used in vivo extracellular single-unit recording and the cells-per-tract technique to evaluate the effects of locally infused hypocretin-1 (orexin A) on VTA dopamine neuron activity. We found that hcrt/orx (0.014 nmol) increased the mean firing rate of VTA dopamine neurons. At 1.4 nmol, hcrt/orx increased the population activity but not the mean firing rate of VTA dopamine neurons. At 140 nmol, hcrt/orx significantly reduced population activity. The reduced population activity was reversed by apomorphine (20 ug/kg), suggesting that hcrt/orx may drive VTA dopamine neurons into a state of depolarization inactivation. The potent excitatory effect of hcrt/orx observed in the present study supports the view that these peptides may play a critical role in goal-directed behaviors by activating the mesolimbic dopamine pathway. The relevance of these findings to goal-directed arousal are discussed.

Disclosures: **J.W. Muschamp** , None; **R.Y. Shen**, None; **E.M. Hull**, None.

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