Yin and Yang of VTA Opioid Signaling. Focus on “Both Kappa and Mu Opioid Agonists Inhibit Glutamatergic Input to Ventral Tegmental Area Neurons”

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In opioid signaling in the brain μ- and κ-opioid receptors (MOR and KOR) are like the yin and yang principles in Chinese philosophy, they always act as an opposing pair. The antagonistic interactions between MOR and KOR are widespread in the CNS. In few receptor families, two closely related members with such overlapping expression in the brain produce such opposite behavioral effects. In humans, MOR agonists cause euphoria, feelings of well-being and liking, whereas KOR agonists produce dysphoria and psychotomimetic effects (Martin 1983). In primates and rodents, MORs mediate the reinforcing effects of heroin and morphine, which are antagonized by KOR agonists (De Vries and Shippenberg 2002; Pan 1998). The well-known analgesic effects of morphine are also conveyed by MORs. KOR agonists, although lightly analgesic by themselves, suppress or abolish MOR-mediated analgesia (Pan 1998; Sora et al. 1997). In contrast to the opposing behavioral effects of MOR and KOR activation, cellular responses and receptor signaling of MOR and KOR are surprisingly similar. Both MOR and KOR agonists hyperpolarize neurons (Johnson and North 1992; Margolis et al. 2003). They both activate G-protein cascades that increase potassium conductance and reduce calcium conductance (Pan 1998). This begs the question that has been driving research on MOR and KOR actions over the last decade: how can activation of these two receptors produce opposing behavioral effects while triggering identical cellular mechanisms?

It has become clear that the answer must lie in cellular distribution of receptors within brain areas. Early indications that network effects are key to understanding opiate drug effects came from studies in the ventral tegmental area (VTA) (Johnson and North 1992). In the VTA, dopaminergic (DA) neurons are situated that project to the nucleus accumbens (NAc) and prefrontal cortex (PFC). This mesolimbic DA system is involved in behavioral reinforcement, and as other drugs of abuse, MOR agonists morphine and heroin enhance DA release in the NAc (De Vries and Shippenberg 2002; Di Chiara and Imperato 1988). In contrast, KOR agonists reduce NAc DA release (Di Chiara and Imperato 1988) and lack reinforcing effects (Dykstra et al. 1997). What are the VTA network mechanisms underlying these opiate effects? On p. 3086–3093 of this issue of the Journal of Neurophysiology, Margolis et al. now add interesting pieces to the puzzle on distributed MOR and KOR signaling in the VTA (Margolis et al. 2005).

Besides DA neurons, the VTA contains GABAergic interneurons as well as GABAergic projection neurons. At first glance, opiate modulation of DA neuron activity appears rather straightforward. MOR activation hyperpolarizes GABA neurons, and as a consequence DA neurons are disinhibited (Johnson and North 1992), thereby explaining the increased NAc DA release. Recently, Margolis et al. showed that KOR agonists hyperpolarize a subset of DA neurons directly (Margolis et al. 2003), nicely explaining the observed decrease in NAc DA release (Di Chiara and Imperato 1988). However, when glutamatergic transmission in the VTA is taken into account, the story becomes more complicated. MOR agonists depress glutamatergic inputs to both VTA DA and GABA neurons (Bonci and Malenka 1999; Manzoni and Williams 1999), thereby most likely reducing activity in these neurons. By carefully teasing apart pre- and postsynaptic effects, Margolis et al. find that both MOR and KOR depress glutamatergic inputs to all VTA cell types. However, MOR agonists reduce glutamatergic inputs to primary DA neurons much more than KOR agonists, and MORs and KORS are most likely segregated to different glutamatergic synapses. In contrast, MOR and KOR actions intermingle on inputs to secondary GABAergic neurons. There, MORs and KORS are most likely located on the same presynaptic terminals and possibly in a fixed ratio because MOR and KOR reduction of glutamatergic inputs are positively correlated. Interestingly, Margolis et al. find that in the primary DA neuron subset that is hyperpolarized by KOR agonists, the effect of MOR agonists on glutamatergic inputs was strongest. And vice versa, in the subset of tertiary GABA neurons, postsynaptic inhibition by MOR agonists is correlated with presynaptic inhibition by KOR activation. Thus it seems that in VTA both MOR and KOR depress excitatory drives to all neuron types either by postsynaptic inhibition, presynaptic inhibition, or both.

What determines the balance? As Margolis et al. suggest, differential regulation of glutamatergic inputs to VTA neurons by MORs and KORS opens the possibility that information from different brain areas is modulated differentially by opioid signaling. In addition, differential pre- and postsynaptic opioid modulation of subtypes of DA and GABA neurons most likely reflects the different projection patterns of these neurons (Carr and Sesack 2000). Alternatively, the balance could be set by the type of firing pattern that neurons exhibit. PFC glutamatergic projections induce burst firing of VTA DA neurons (Murase et al. 1993), whereas decreased glutamate levels induce regular firing patterns. Burst firing is twice as effective in augmenting DA release in NAc (Suaud-Chagny et al. 1992). It remains to be tested what type of firing pattern MOR
reduction of glutamatergic inputs to DA neurons will induce. One of the big questions that remains to be addressed is what mechanism underlies morphine-induced LTP to VTA DA neurons. Virtually all classes of abused drugs induce LTP in the VTA in vivo, and this is thought to be involved in the early drug-induced behavioral changes (Bonci et al. 2003). For some of these drugs, candidate synaptic and cellular mechanisms are apparent (Bonci et al. 2003; Mansvelder and McGehee 2000; Mansvelder et al. 2002), but it will be exciting to learn how the acute depression of VTA glutamatergic inputs induced by morphine results in a long-term upregulation of synaptic strength.

REFERENCES


