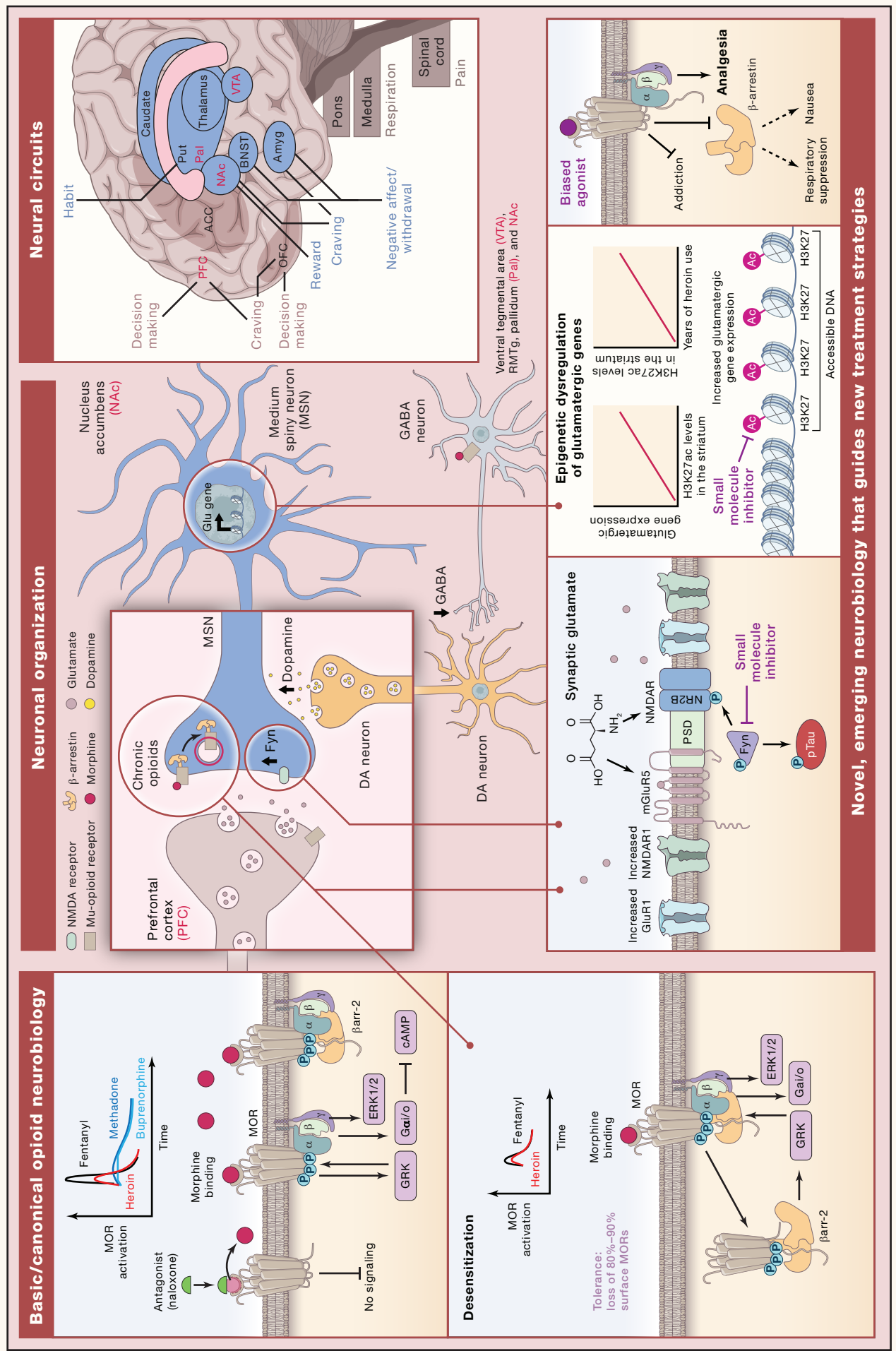


SnapShot: Neurobiology of opioid use disorder

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Novel, emerging neurobiology that guides new treatment strategies

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Acute opioid neurobiology

Opioid drugs exhibit varying potency, efficacy, and pharmacokinetics at opioid receptors—mu (MORs), delta (DORs), and kappa (KORs)—an inhibitory class of G protein-coupled receptors (GPCRs). MORs and DORs mediate the analgesic and rewarding/addictive properties of opioids, whereas KORs have limited clinical analgesic properties due to undesirable effects such as dysphoria, anxiety, and hallucinations. We focus on MORs, the target of most opioid use disorder (OUD)-related research. MOR agonists lead to $G_{\alpha_{i/o}}$ activation, cAMP inhibition, receptor internalization, receptor phosphorylation by G protein receptor kinase (GRK), and recruitment of β -arrestin 2 (β arr-2) and other downstream effectors including enzymes, ion channels, and small GTPase, thus regulating multiple signaling pathways including the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) phosphorylation cascade (Williams et al., 2013).

Recreational opioids such as heroin and prescription opioids (e.g., morphine, codeine, and oxycodone) are full MOR agonists. High-potency, synthetic opioids such as fentanyl are highly rewarding and exacerbate opioid overdose deaths. The actions of opioids and opioid-induced overdoses can be reversed by high-affinity MOR antagonists (e.g., naloxone) that displace opioids and inactivate MORs.

Chronic opioid neurobiology

With repeated opioid administration, tolerance occurs such that drug effects (analgesia, reward) are reduced, requiring higher doses to achieve similar effects as previous lower doses (Williams et al., 2013). Chronic use of opioids also leads to long-lasting alteration of other transmitter systems (e.g., dopamine [DA], glutamate, and GABA) contributing to altered synaptic plasticity. For example, chronic MOR activation increases surface expression of glutamatergic receptors (AMPA and NMDA receptor subunits), key regulators of synaptic function (Chartoff and Connery, 2014).

Neuronal organization and neural circuits

MORs are widely expressed in brain, including structures highly implicated in addiction. The mesolimbic reward pathway consists of the midbrain ventral tegmental area (VTA) and nucleus accumbens (NAc; ventral striatum). Direct activation of MORs in the NAc has positive hedonic properties. VTA DA neurons, which mediate reward, are regulated by GABAergic VTA interneurons and to a greater extent by GABA neurons originating from regions with abundant MOR expression including NAc, rostromedial tegmental nucleus (RMTg), and ventral pallidum (Galaj and Xi, 2021). Opioid activation of MORs reduces the release of GABA, an inhibitory neurotransmitter, thereby disinhibiting VTA DA neurons, resulting in excitation and increased DA levels in the NAc contributing to the acute rewarding effects of opioids (Johnson and North, 1992).

The dorsal striatum (caudate and putamen [Put]), which receives abundant midbrain DA input, plays a critical role in habitual behavior that emerges with opioid abuse. Similar to other drugs of abuse, chronic opioid use dysregulates glutamatergic processes relevant to synaptic plasticity (Kruyer et al., 2020). The prefrontal cortex (PFC), which includes the orbital frontal cortex (OFC), mediates decision-making, reward value, and goal-directed behavior, providing top-down glutamatergic regulation of subcortical regions as the NAc, dorsal striatum, and amygdala (Amyg). PFC and NAc activity is increased during drug craving in humans. Consistently, the PFC-NAc circuit is implicated in cue-induced reinstatement behavior in heroin self-administration animal models coinciding with increased NAc glutamate levels (Kruyer et al., 2020). The Amyg is also highly involved in emotional dysregulation of craving and negative affect often manifested during withdrawal.

Clinically, MOR agonists are important analgesics due to their ability to inhibit pain signals in the dorsal horn of the spinal cord. However, the increased use of opioids, as tolerance develops, and the use of highly potent drugs such as fentanyl increases overdose risk that can be fatal due to inhibition of the brainstem respiratory centers in the medulla and pons that have abundant MORs (Montandon and Horner, 2014).

Novel, emerging neurobiology

The dysregulation of the glutamatergic system seen with chronic opioid use is a growing area of research focus. Recent molecular evidence highlights epigenetic disturbances in the striatum of human heroin abusers linked to the nonreceptor tyrosine kinase Fyn that regulates glutamatergic signaling and cytoarchitectural organization (Egervari et al., 2020). FYN disturbances in striatal neurons in human heroin abusers are mimicked in rodents that self-administer heroin. Heroin increases both the active (phosphorylated) form of Fyn and phosphorylation (Tyr-18) of its downstream target Tau, highly implicated with neurocognitive decline. Studies of the human brain also emphasize epigenetic impairments of genes related to synaptic plasticity and glutamatergic neurotransmission that significantly correlate with certain epigenetic marks, e.g., H3K27 acetylation, which positively correlate with the years of heroin use (Egervari et al., 2017).

Conventional and novel theories for OUD treatment

Current standard treatments for OUD consists of substitution with another opioid with lower potency and longer half-life, such as methadone, to prevent periods of highs and withdrawal. Buprenorphine is also used clinically and is often formulated with naloxone (Suboxone) to block rewarding effects if inappropriately taken intravenously rather than orally.

Novel opioid ligands are evolving that attempt to leverage distinct intracellular signaling pathways that might differentially mediate MORs' effects on reward, analgesia, and respiratory suppression. For example, G protein signaling and β -arrestin recruitment mediate analgesia and respiratory suppression, respectively (Schmid et al., 2017), whereas reward is driven by GRK-5 (Glück et al., 2014). This suggests that biased agonists, which stabilize MOR in a conformation that selectively activates a particular intracellular signaling cascade, might serve as potent analgesics without increasing addiction risk.

The need for non-opioid medications has also brought focus to the glutamatergic system. For example, a small molecule inhibitor of Fyn kinase reduces heroin-taking behavior in pre-clinical animal models (Egervari et al., 2020). Similarly, an inhibitor of acetylation epigenetic marks, associated with impaired glutamatergic signaling, decreases heroin self-administration (Egervari et al., 2017).

These and other emerging neurobiological findings relevant to OUD could offer new treatment strategies to significantly curb the opioid epidemic and help millions suffering from the disorder.

REFERENCES

- Chartoff, E.H., and Connery, H.S. (2014). It's MORe exciting than mu: Crosstalk between mu opioid receptors and glutamatergic transmission in the mesolimbic dopamine system. *Front. Pharmacol.* 5, 116.
- Egervari, G., Landry, J., Callens, J., Fullard, J.F., Roussos, P., Keller, E., and Hurd, Y.L. (2017). Striatal H3K27 Acetylation Linked to Glutamatergic Gene Dysregulation in Human Heroin Abusers Holds Promise as Therapeutic Target. *Biol. Psychiatry* 81, 585–594.
- Egervari, G., Akpoyibo, D., Rahman, T., Fullard, J.F., Callens, J.E., Landry, J.A., Ly, A., Zhou, X., Warren, N., Hauberg, M.E., et al. (2020). Chromatin accessibility mapping of the striatum identifies tyrosine kinase FYN as a therapeutic target for heroin use disorder. *Nat. Commun.* 11, 4634.
- Galaj, E., and Xi, Z.X. (2021). Progress in opioid reward research: From a canonical two-neuron hypothesis to two neural circuits. *Pharmacol. Biochem. Behav.* 200, 173072.
- Glück, L., Loktev, A., Moulédous, L., Mollereau, C., Law, P.Y., and Schulz, S. (2014). Loss of morphine reward and dependence in mice lacking G protein-coupled receptor kinase 5. *Biol. Psychiatry* 76, 767–774.
- Johnson, S.W., and North, R.A. (1992). Opioids excite dopamine neurons by hyperpolarization of local interneurons. *J. Neurosci.* 12, 483–488.
- Kruyer, A., Chioma, V.C., and Kalivas, P.W. (2020). The Opioid-Addicted Tetrapartite Synapse. *Biol. Psychiatry* 87, 34–43.
- Montandon, G., and Horner, R. (2014). CrossTalk proposal: The preBotzinger complex is essential for the respiratory depression following systemic administration of opioid analgesics. *J. Physiol.* 592, 1159–1162.
- Schmid, C.L., Kennedy, N.M., Ross, N.C., Lovell, K.M., Yue, Z., Morgenweck, J., Cameron, M.D., Bannister, T.D., and Bohn, L.M. (2017). Bias Factor and Therapeutic Window Correlate to Predict Safer Opioid Analgesics. *Cell* 171, 1165–1175.e13.
- Williams, J.T., Ingram, S.L., Henderson, G., Chavkin, C., von Zastrow, M., Schulz, S., Koch, T., Evans, C.J., and Christie, M.J. (2013). Regulation of m-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. *Pharmacol. Rev.* 65, 223–254.