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Modulation of alcohol and nicotine responses through the endogenous opioid system

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ABSTRACT

It has been estimated that more than 80% of alcoholics are also nicotine dependent and that, vice versa, the rate of alcoholism is substantially increased by a factor of 4–10 in the nicotine-dependent population. However, the cause for this very high degree of comorbidity is still largely unknown. At the molecular and cellular level, both drugs have very different mechanisms of action. Nicotine specifically activates ligand-gated ion channels in the brain, which are normally gated by acetylcholine, while alcohol interacts with various neurotransmitter receptors. Despite this diversity, both drugs seem to engage the endogenous opioid system as a modulator of some of its pharmacological effect. An acute exposure to nicotine or alcohol leads to a release of opioid peptides in specific brain regions, thus resulting in an activation of their corresponding receptors. If the brain is exposed repeatedly or chronically to these drugs, adaptive changes in the level and expression of opioid peptides and receptors occur. These adaptive changes are thought to contribute to the homeostatic or allostatic adaptations of the brain, which have been associated with drug dependence. This review summarizes pharmacological and genetic studies in animal models and in humans that have addressed the role of specific opioid peptides and receptors in various stages of the addiction process.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine-3 (serotonin); ACTH, adrenocorticotrophic hormone; ADE, alcohol deprivation effect; COGA, Collaborative Study on the Genetics of Alcoholism; CPA, conditioned place aversion; CPP, conditioned place preference; DAMGO, [D-Ala2,N-Me-Phe4,Gly-ol5]-enkephalin; GABA, γ-aminobutyric acid; MSH, γ-melanocyte stimulating hormone; NAc, nucleus accumbens; nAChR, nicotinic acetylcholine receptor; NMDA, *N*-methyl-D-aspartic acid; nor-BNI, nor-binaltorphimine; PAG, periaqueductal grey; PDYN, preprodynorphin; PENK, preproenkephalin; POMC, proopiomelanocortin; PR, progressive ratio; QTL, quantitative trait loci.

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"Smokers drink and drinkers smoke" is not only a popular expression, but also an unfortunate well-documented fact. Smoking in adolescents is the strongest predictor for alcohol-related problems in later life (Riala et al., 2004). When compared to the general population, people who are addicted to smoking are four times more likely to be also dependent on alcohol, while nicotine dependence is three times higher in people addicted to alcohol (Grant et al., 2004). Moreover, tobacco consumption is positively correlated with the degree of alcohol dependence and the amount of alcohol consumed. A practical consequence of this high degree of comorbidity is the observation that alcoholics are more likely to succumb to smoking-related illnesses rather than to alcohol-related health problems, due to the high morbidity associated with tobacco smoking (Littleton et al., 2007).

An important question is why these two substance dependencies show such a high comorbidity. Is it just because nicotine and alcohol are both readily and legally available, or are there also biological reasons? Both drugs have predominantly different molecular mechanisms of action and produce different pharmacological effects. Nicotine activates specific brain receptors, the nicotinic acetylcholine receptors (nAChR), while alcohol acts on several different receptor types. Nevertheless, research in the last two decades has provided a substantial amount of evidence that both drugs affect, indirectly, similar molecular and neuronal systems. The molecular and cellular mechanisms underlying nicotine and alcohol addiction, as well as the genetic risk factors, therefore seem to have some commonality. This review focuses on the endogenous opioid system as a downstream signaling system that is modulated by nicotine and alcohol. We summarize findings from pharmacological and genetic studies to demonstrate that the acute administration of both drugs affects opioid signaling, while chronic exposure leads to adaptive changes in the opioid system that may be associated with nicotine and alcohol addiction. Further, we show that both drugs have similar effects on the activity of the opioid system after acute and chronic administration, and after drug withdrawal, although their molecular mechanisms of action are quite different.

1. The opioid system

Opiates collectively refer to drugs derived from the poppy plant *Papaver somniferum*, which includes morphine, codeine and other structurally related semi-synthetic compounds. Opioids include all drugs and endogenous substances with morphine-like activity.

The first opioid peptide was identified in the 1970s' and termed endorphin by Eric Simon. Molecular cloning has shown that the opioid peptides (endorphin, enkephalin and dynorphin) are generated from precursor proteins encoded by three different genes (Evans et al., 1992; Kieffer et al., 1992; Kieffer and Evans, 2009). They all share the common N-terminal sequence Tyr-Gly-Gly-Phe. This sequence is extended in [Met] enkephalins by either a methionine, or in [Leu]enkephalins by a leucine. Both peptides are derived from the preproenkephalin (PENK) precursor. The preprodynorphin (PDYN) precursor can also be processed to yield [Leu]enkephalin, in addition to the further extended dynorphins. Proopiomelanocortin (POMC) is a multifunctional protein precursor that gives rise to β-endorphin – an opioid peptide of 31 amino acids further extended from [Met] enkephalin – adrenocorticotrophic hormone (ACTH), γ-melanocyte stimulating hormone (MSH), and β-lipotropic hormone.

Opioid peptides activate G-protein-coupled μ-, δ- and κ-opioid receptors, which differ in their affinities and response profiles. The μ-opioid receptor is activated by β-endorphin and probably also by enkephalin, while δ-opioid receptors are activated by enkephalin and to a lesser extend by β-endorphin. Dynorphins bind specifically to the κ-opioid receptor (Akil et al., 1984; Kieffer, 1995). Opioid receptors are widely expressed throughout the brain, including brain regions involved in drug reward and addiction, such as the extended amygdala, ventral tegmental area and nucleus accumbens (see Box 1) (Minami and Satoh, 1995). There is now increasing evidence that opioid receptors, like other G-protein-coupled receptors, form homomeric and heterodimeric complexes in the cell membrane, even with non-opioid receptors (Evans, 2004). How dimerization affects the pharmacological properties of the receptors is currently a topic of intense research in the field.

Research on the endogenous opioid system has substantially contributed to our understanding of the brain substrates and

Box 1. Drug addiction and brain reward.

Early addiction theories already suggested that the initiation of drug abuse is driven by the ability of the drug to produce a pleasurable effect (Wise, 1980). Such effects are commonly termed "**reward**", and the recurrent urge to reach rewarding states builds the basis for the development of dependence (Feltenstein and See, 2008). Often the term reward is misused or confused with the term **reinforcement** (or reinforcer). In behavioral science, reinforcement is the process of strengthening a certain response that follows the presentation of a distinct stimulus, which means that some stimuli (reinforcers) possess the ability to change the occurrence probability of specific behavioral patterns. In general, drugs act as reinforcers and thus they increase the likelihood of responses that produce them, which in turn results in repeated drug taking. The expression reward emerged within the field of experimental psychology and has two additional meanings (Sanchis-Segura and Spanagel, 2006): it can be used as it would be used in a non-scientific context to describe stimuli with appetitive (desirable) consequences. Also reward is used to refer to a hypothetical pleasurable internal state (hedonia), which derives from the acquisition, use or consumption of appetitive stimuli. In this regard, reward or also 'liking' refers to the subjective responses associated with the consequences of afore presented reinforcers, becoming later on important characteristics of the internal representation of these stimuli (Everitt and Robbins, 2005; Sanchis-Segura and Spanagel, 2006).