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The opioid systems – Panacea and nemesis

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ABSTRACT

This mini-review outlines the opioid systems and their roles primarily as related to reward and compulsive drug/alcohol intake. The central role is taken by the mu-opioid receptor, target for opiate analgesics and also a central target in compulsive alcohol abuse, alcoholism. The mu-opioid receptor and the cognate opioid neuropeptides from proenkephalin and proopiomelancortin are members of a superfamily of opioid systems, each with unique and still to be defined roles in the central nervous system.

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1. A short historical account

The discovery of a unique opiate receptor (and not just an "artificial site" on another receptor) and the linked discovery of a previously unknown group of endogenous neuropeptides with opioid activity was undoubtedly a paradigm shift in the 1970s, that influenced and still influences our view on the nature of pain and how to treat pain. Significantly, the role of these neuropeptides with regard to reward and drug/alcohol dependence is also being clarified.

The idea that pain is context-dependent is not new. Severe pain always has an existential dimension and stressful reactions contribute to the severity. Therapeutically, various procedures, collectively known as "counter-irritation", the best known being acupuncture have a long history. An attempt to rationalize these observations was the "gate control theory" [1] which based on electrophysiological analysis identified local and descending neuronal pathways in the dorsal horn of the spinal cord which receives afferent influx from nociceptive nerve fibers. Histologic analysis confirmed the strategic localization of enkephalin (opioid) neuropeptides in local interneurons terminating presynaptically on the substance P-containing afferent neurons (C-fibers) [2].

Further histologic analysis showed the presence of enkephalin peptides at supraspinal levels in areas relevant to pain. This is not surprising since opiates affect the subjective feeling of pain, "I still have severe pain but it does not bother me as much as before". In fact, opiates are not just pain-reducing substances, they are psychotrophic agents with wide-spread effects on emotional (tranquilizing) and motivational states. The use of opium as a tranquilizer and euphorigenic agent has at least a 5000 year history. When the active principle in opium, morphine was isolated by Sertürner [3], he gave it the name in recognition of the Greek God of Sleep. To account for the effects of opiates, a receptor named mu (for morphine) was introduced, in current terminology named MOP.

The central role of opiates for pain relief and intravenous anesthesia generated a wealth of medicinal chemistry to identify synthetic congeners. A substantial contribution was made by German scientists during World War II when Germany had no access to opium [4]. Pharmacologic analysis also identified compounds with nonclassical activities, some of which reached clinical trials. The most interesting compounds acted on a receptor named "kappa" (for ketocyclazocine). Recent terminology is KOP.

2. The endogenous opioid systems

The discovery of the enkephalins, opioid pentapeptides opened up two lines of research. These peptides are conveniently short, and they could be easily modified by changes in amino acid sequence or introduction of artificial amino acids to protect from enzymatic degradation. Virtually, thousands of enkephalin analogues have been synthesized and evaluated. A large amount of structure–activity (SAR) studies have identified significant positions in leu-enkephalin, (TyrGlyGlyPheLeu, the N-terminal Tyr and the Phe residues are critical whereas the C-terminus can accommodate Met, which occurs naturally or other amino acids). Besides opening the road for a new avenue in neuropeptide studies, the enkephalin pharmacology identified a delta-receptor (DOP). A fourth member in the family, primarily labeled ORL-1 (orphan receptor-like-1) was later used to identify a natural ligand, which was named nociceptin since it showed "pain-like" activity in certain assays. The nociceptin receptor is now named NOP (Table 1).

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Table 1
Some of the major opioid peptides, their precursor proteins and preferred receptors.

Precursor	Typical peptide	Preferred receptor
Proenkephalin	Leu-enkephalin* Met-enkephalin*	MOP (opiate), DOP
Proopiomelanocortin[1]	β-Endorphin*	MOP, DOP
Prodynorphin	Dynorphins A* and B*	KOP
Pronociceptin	Nociceptin[2]	NOP

* Opioid peptides.
[1] Also precursor to ACTH and MSH acting on non-opioid receptors.
[2] Structurally related to the opioid peptides. Not an opioid peptide according to the strict definitions.

The classification of nociceptin as an opioid peptide is based entirely on structural similarity (Table 2). All four receptors are structurally related with homology exceeding 70%. It came as a disappointment that the enkephalins and β-endorphin also are addictive. In fact self-administration experiments indicated that a metabolically stable enkephalin derivative was equally addictive as morphine [5]. In most assays, activation of MOP or DOP give very similar effects and these receptors are sometimes co-existing in the same neurons.

All receptors in the opioid superfamily are coupled to G-proteins (GPCRs) and cause hyperpolarization (inhibition) of neurons. KOP is also G-protein coupled, but differs from the others in that it activates a separate signal transduction pathway. KOP agonists are also behaviorally different, they are aversive and not subject to self-administration. In fact some opioid agonists also have affinity for KOP. The still used opiate antidote naloxone and the anaesthetic ketamine are known to have side effects including hallucinations probably through KOP which preclude their wide-spread use. The authors' laboratory has even suggested that dynorphin peptides may be responsible for positive symptoms in psychosis. Clinical testing of the hypothesis has not given convincing results, however.

The access to genetic modifications has also been applied to the opioid systems. For instance genetic elimination of MOP [6] or KOP [7] in mice attenuates self-administration of alcohol.

A recent paper has addressed the evolution of the opioid superfamily system. The full repertoire (all four precursors to the peptides and all four receptors) are already present approximately 450 million years ago. So far all investigated species have been found to have the full quartet receptor and precursor families [8]. It is probably significant that the opioid receptors are comparatively short as compared with other GPCRs.

3. The reward system

The basic drives for food, water or sex generate a feeling of reward. Mainly due to the work of James Olds and colleagues, it was found that a rat able to activate electrodes implanted in certain brain areas would also be rewarded [9]. This artificial activation of an endogenous mechanism opens a window to reinforcement of intake of alcohol and drugs that can be studied in the laboratory. Numerous studies have been performed that have identified a central dopamine pathway, the mesolimbic pathway from the ventral tegmental area (VTA) projecting to the nucleus accumbens (NA). Drugs of abuse, essentially without exception activate this pathway, considered as the common denominator for addictive drugs [10]. A complicating factor is that the large numbers of drugs affecting the dopamine receptors are often not active in experimental settings in laboratory animals and are not recognized for human use. One possible explanation is that there are several parallel pathways that are relevant for reward. Complementary studies with microinjections have identified strong reinforcement of opiate self-administration either in the VTA or the NA. Microinjection into the NA is probably acting directly without dopamine mediation [11]. The mesolimbic dopamine pathway projects onto a pathway to the frontal cortex, which in primates including man, is strongly activated by substances of abuse including opiates and cocaine [12]. An overwhelming amount of data suggests that the reward center is instrumental in positive reinforcement and opens the way to dependence. In the dependent stage, other pathways and systems may be more relevant.

Table 2
Sequence comparison of dynorphin A and nociceptin (using one-letter nomenclature for amino acid residues). Identical amino acids residues are indicated by a hyphen.

Dynorphin A	YGGFLRRIRPKLKWDNQ
Nociceptin	F–TGARKSAR-LA–

4. The allostasis of addiction

The career to become dependent on alcohol or drugs is gradual. In general terms, early exposure is changing the emotional homeostasis (with its ups and downs) to a protracted state that is hard to escape from.

To conceptualize the altered stage, Koob and Le Moal have introduced the term allostasis, [13]. This state is reached by feed-forward mechanisms no longer accessible to homeostatic counter-balancing effects that under "normal" circumstances keep the reward system under control. Allostasis is characterized by emotional distress and dysphoria, and it has been suggested from animal experiments that reinstatement of drug/alcohol intake ("relapse") is due to increase in activity the dynorphin/KOP axis [14,15].

Another useful concept is "brain stress" to describe the altered state. Several neuropeptide systems may be involved including dynorphin/KOP as stress mediator and nociceptin/NOP as anti-stress mediator. The authors' laboratory showed that a nociceptin agonist suppresses alcohol preference [16]. The extended amygdala has been implicated [17].

5. The dynamics of opioid systems

Reward is "functional" in the physiologic sense to encourage activities that are essential to the survival of the individual, such as food and water, or the species, sex. The sense of reward is not functional if it becomes protracted; in fact MOP is rapidly down-regulated after repeated exposure to an opioid, mainly due to internalisation and degradation. Nature has not designed the MOP to sustain short-circuiting as occurs in alcohol/drug abuse. Blocking MOP with naltrexone suppresses the incentive in rodents to drink alcohol and is used clinically as ReVia® to reduce craving for alcohol. Further strengthening the role of MOP in the prevention of relapse is an association of isoforms of the receptor at position 40 (Asn40Asp) with treatment efficacy [18]. This is an almost unique example of interindividual differences in psychotrophic therapy outcome based on genetic differences in a target gene which opens the potential of personalized medicine.

The dynamics of the opioid receptor systems extend to studies at the molecular level. Recent work from the authors' laboratory has studied molecular dynamics of fluorescently-labeled opioid receptors using a unique instrument for fluorescence correlation spectroscopy/confocal laser scanning imaging (FCS/CLSM). The opioid receptors are highly mobile and migrate laterally in the plasma membrane at two (or more) rates, suggesting "free" movement or movement associated with partners, either lipids or other proteins. Most studies have been performed with MOP. Binding of an

agonist, such as morphine or enkephalin accelerates mobility. On the contrary, the antagonist naltrexone "freezes" the receptor in the membrane and slows down lateral movement. Significantly enkephalin rapidly induces receptor internalization (and degradation) to protect the cell from sustained activation, whereas morphine is much less active, which may contribute to its abuse potential [19]. Ethanol at relevant concentrations (10–40 mM) induces an intermittent accumulation of MOP in the plasma membrane, besides affecting lipid (cholesterol) dynamics [20]. In an emerging model, a dynamic interaction between MOP and the semicrystalline cholesterol matrix in the plasma membrane is proposed; not only does ethanol modulate MOP mobility; the reverse is also true, MOP agonists by changing receptor conformation change lipid dynamics. These reciprocal interactions may also explain the anaesthetic properties of MOP agonists.

6. Back to the future

The classic opiates including morphine remain cornerstones in the pharmacologic armamentarium. Severe chronic pain is evil and opiates are the only rational medications. They primarily target MOP, which has a critical location in brain and spinal cord areas relevant to severe pain. Based primarily on clinical observations, the MOP antagonist naltrexone (ReVia®) can prevent relapse in alcoholism, suggesting a role of MOP in addictive behaviors. Experimental data suggest that "anti-reward" opioid systems with KOP and NOP receptors may have developed to counterbalance. These systems could become targets for pharmacotherapy of addictions in the future.

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