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Opioids: cellular mechanisms of tolerance and physical dependence

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Morphine and other opioids are used and abused for their analgesic and rewarding properties. Tolerance to these effects develops over hours/days to weeks, as can physical and psychological dependence. Despite much investigation, the precise cellular mechanisms underlying opioid tolerance and dependence remain elusive. Recent studies examining μ-opioid receptor desensitization and trafficking have revealed several potential mechanisms for acute receptor regulation. Other studies have reported changes in many other proteins that develop during chronic opioid treatment or withdrawal and such changes may be partly responsible for the cellular and synaptic adaptations to prolonged opioid exposure. While these studies have added to our knowledge of the cellular processes participating in opioid tolerance and dependence, the challenge remains to integrate these observations into a coherent explanation of the complex changes observed in whole animals chronically exposed to opioids.

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Abbreviations

AC	adenylyl cyclase
CREB	cAMP response element binding protein
DAMGO	[D-Ala2, N-Me-Phe4, Gly5-ol]-enkephalin
DOR	δ-opioid receptor
GABA	γ-aminobutyric acid
GAT-1	GABA transporter
GRK	G-protein-coupled receptor kinase
LC	locus coeruleus
MAPK	mitogen-activated protein kinase
MOR	μ-opioid receptor
NK_1	neurokinin-1 receptor
PAG	periaqueductal grey
PLD_2	phospholipase D_2

Introduction

Opioid drugs are used clinically as unsurpassed analgesic agents but are also illegally abused on the street to induce a sense of well-being and euphoria. Tolerance to opioids, defined as a loss of effect following repeated treatments such that a higher dose is required for equivalent effect, limits the analgesic efficacy of these drugs [1] and contributes to the social problems surrounding recreational opioid abuse. In animals, tolerance to the anti-nociceptive effects of opioids can be observed even after a single dose, and continues to develop over many weeks of drug treatment. A complex interplay of events occurring at the single cell level and also in neuronal networks are likely to contribute to whole animal opioid tolerance, with distinct mechanisms being more important at different times during chronic exposure.

This review summarizes key recent advances in our understanding of the mechanisms underlying the phenomenon of cellular tolerance, which is the reduced response to opioid agonists by μ-opioid receptor (MOR)-expressing neurons during chronic agonist exposure. Cellular tolerance following prolonged opioid receptor activation could result from alterations in receptor coupling, receptor number, the amount of effector protein or the capacity of an effector to be regulated by opioid receptors. Recent work has focused largely on the idea that the capacity of agonists to recruit various MOR regulatory events is a major determinant of their propensity to induce both tolerance and dependence. Concurrent work is increasingly promoting the idea that tolerance and dependence/withdrawal are molecularly separable phenomena, and therefore this review also covers recent studies examining possible cellular substrates of physical dependence, including adaptations unmasked on withdrawal from chronic opioid treatment.

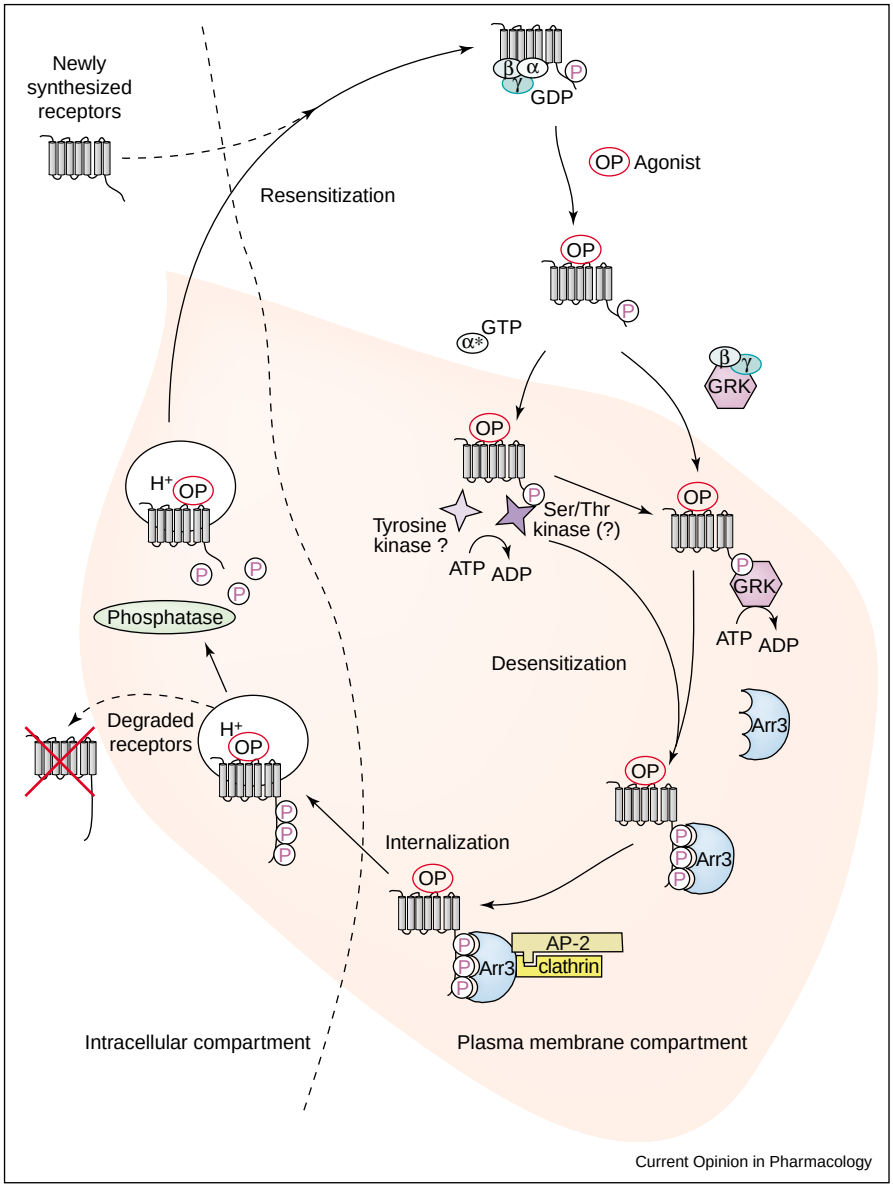
Receptor desensitization and trafficking

The analgesic and rewarding properties of opioid drugs occur through activation of MORs [2]. MORs are $G_{i/o}$-coupled receptors and, like many other G-protein-coupled receptors, can undergo rapid desensitization and internalization following exposure to agonist [3•,4,5]. These acute receptor regulatory processes have assumed a central role in discussions into the development of cellular tolerance to morphine and other MOR agonists [4]. The generally accepted mechanism underlying MOR desensitization and internalization begins with phosphorylation of activated receptors by G-protein-coupled receptor kinases (GRKs), followed by arrestin binding. At this point, the

receptor is in a desensitized state at the plasma membrane. Arrestin-bound receptors can then be internalized via a clathrin-dependent pathway, and either recycled to the cell surface or downregulated [3•,4,6] (Figure 1).

In heterologous expression systems, opioid receptor desensitization can also be modulated by second messenger-linked protein kinases such as protein kinase C, protein kinase A and calcium/calmodulin-dependent kinase II [7]. The relative importance of different kinases in regulating opioid receptor activity in neurons has not yet been resolved, and the potential interactions between second-messenger-linked protein kinases, GRKs and arrestins in MOR desensitization, internalization and

Figure 1



Pathways for acute μ-opioid receptor regulation. The phenomena of opioid receptor activation, uncoupling and internalization are well described, but the precise mechanisms underlying the experimental observations are largely undefined. The pink shaded area represents states of the receptor that are likely to be uncoupled from signalling. Although it is assumed that once MOR is phosphorylated and bound by arrestin it is functionally desensitized, alternative mechanisms of desensitization might also occur. Opioid receptors are basally phosphorylated, but the kinases responsible for this are unknown. A role for serine/threonine protein kinases such as protein kinase A, calmodulin-dependent protein kinase and protein kinase C in receptor desensitization and/or the recruitment of GRK-dependent receptor trafficking have been suggested, but they have yet to be defined in detail. Similarly, specific tyrosine kinases that phosphorylate the MOR have not been identified. Approximately 80% of MORs that undergo endocytosis are recycled; the remaining 20% are degraded in lysosomes. AP-2, adaptor protein 2; Arr3, arrestin-3; P, phosphate.