Chapter 66
Endogenous Opioids, Opioid Receptors, and Incentive Processes

Mauricio R. Papini and Leonardo A. Ortega

Abbreviations

cE	Consummatory extinction
CNS	Central nervous system
cSNC	Consummatory successive negative contrast
DOR	Delta opioid receptor
EFF	Escape from frustration
iE	Instrumental extinction (operant lever pressing)
iSNC	Instrumental successive negative contrast
KOR	Kappa opioid receptor
MOR	Mu opioid receptor
ORL-1	Opioid-receptor-like receptor
pE	Pavlovian extinction (autoshaped lever pressing)

66.1 Introduction

Endogenous opioid peptides and their receptors are involved in the modulation of a variety of behavioral functions because of their relatively diffuse distribution in the CNS. Recent research suggests that endogenous opioids modulate incentive processes. Incentives are environmental resources that motivate the organism to behave. Incentive motivation is activated by expectancies which, in turn, are the result of learning and memory processes. Thus, the study of endogenous opioids in relation to incentive processes encompasses behavioral topics including motivation, emotion, learning, and memory (Table 66.1).

66.2 Opioid Peptides and Receptors

Endogenous opioid peptides consist of short sequences of amino acids synthesized from precursor polypeptides. There are five major groups of opioid peptides, and their precursors are known for four of them (Table 66.2). A model example of the posttranslational changes that result in the sequential

M.R. Papini (✉)
Department of Psychology, Texas Christian University, Fort Worth, TX 76129
e-mail: m.papini@tcu.edu

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Table 66.1 Key features of opioid system and incentive processes

1. The four types of opioid receptors are diffusely distributed in the mammalian brain, thus playing a role in many different behavioral processes.
2. Opioid peptides and their receptors have significant functions in relation to incentive processes, i.e., the attribution of hedonic value to environmental resources such as food and fluids.
3. Incentive value can be viewed in an absolute (e.g., food palatability) or relative manner (e.g., incentive contrast effects).
4. Food palatability, also known as food liking (as different from food wanting), depends on the degree of opioid activation during consummatory behavior.
5. Endogenous opioids are naturally released during episodes involving the unexpected omission or devaluation of food reinforcers (incentive contrast).
6. The initial reaction to incentive contrast involves DORs, whereas the recovery from incentive contrast involves KORs.

This table lists the key facts about the relationship between endogenous opioids, opioid receptors, and incentive processes

Table 66.2 Precursors and products

Precursor	Peptide
Pro-opiomelanocortin	γ-MSH (melanocyte stimulating hormone)
	ACTH (adrenocorticotropic hormone)
	α-MSH (melanocyte stimulating hormone)
	γ-LPH (lipotropin hormone)
	β-LPH (lipotropin hormone)
	β-endorphin
Pro-enkephalin	Met-enkephalin
Pro-dynorphin	Dynorphin A
	Dynorphin B
	Neoendorphin
Pro-nociceptin	Nociceptin/orphanin
(Unknown)	Endomorphin-1
	Endomorphin-2

This table illustrates the polypeptide precursors and their opioid and nonopioid products

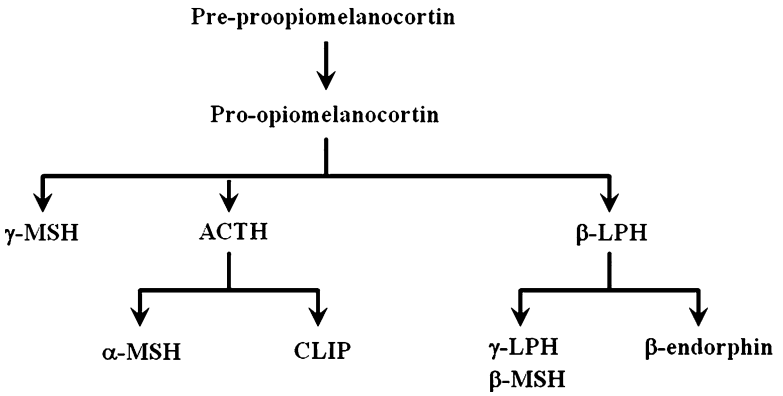

Fig. 66.1 Gene products of pre-proopiomelanocortin. Cleavage of opioid and nonopioid peptide products from the pre-proopiomelanocortin gene

cleavage from an opioid precursor is provided by proopiomelanocortin (POMC) in Fig. 66.1. The pre-proopiomelanocortin gene codes for the precursor POMC. This gene contains 7,665 bp in three exons and two introns (Raffin-Sanson et al. 2003). The resulting polypeptide, consisting of 241 amino acids, is processed and, depending upon the enzymes present, cell-specific patterns of cleavage

generate the opioid peptides β-endorphin and β-lipotropin, as well as nonopioid peptides such as the adrenocorticotropic hormone (ACTH), other lipotropins (LPH), corticotropin-like intermediate peptide (CLIP), and different types of melanocyte-stimulating hormones (MSH).

Opioid receptors are G-protein-coupled receptors that exhibit a high degree of structural similarity (Lord et al. 1977; Sim-Selley et al. 2003). Four opioid receptors have been identified and are known as MOR, KOR, DOR, and ORL-1 (also known as nociceptin opioid peptide receptor). These receptors are distributed throughout the CNS, with somewhat differential concentrations of each receptor across brain areas (Fig. 66.2) (Mansour et al. 1995; Sim-Selley et al. 2003). They have been described in mammals, birds, reptiles, amphibians, and teleost fish, but not in chondrichthyes (sharks), cephalochordates (lancelets), urochordates (tunicates), or arthropods (fruit fly) (Dreborg et al. 2008;

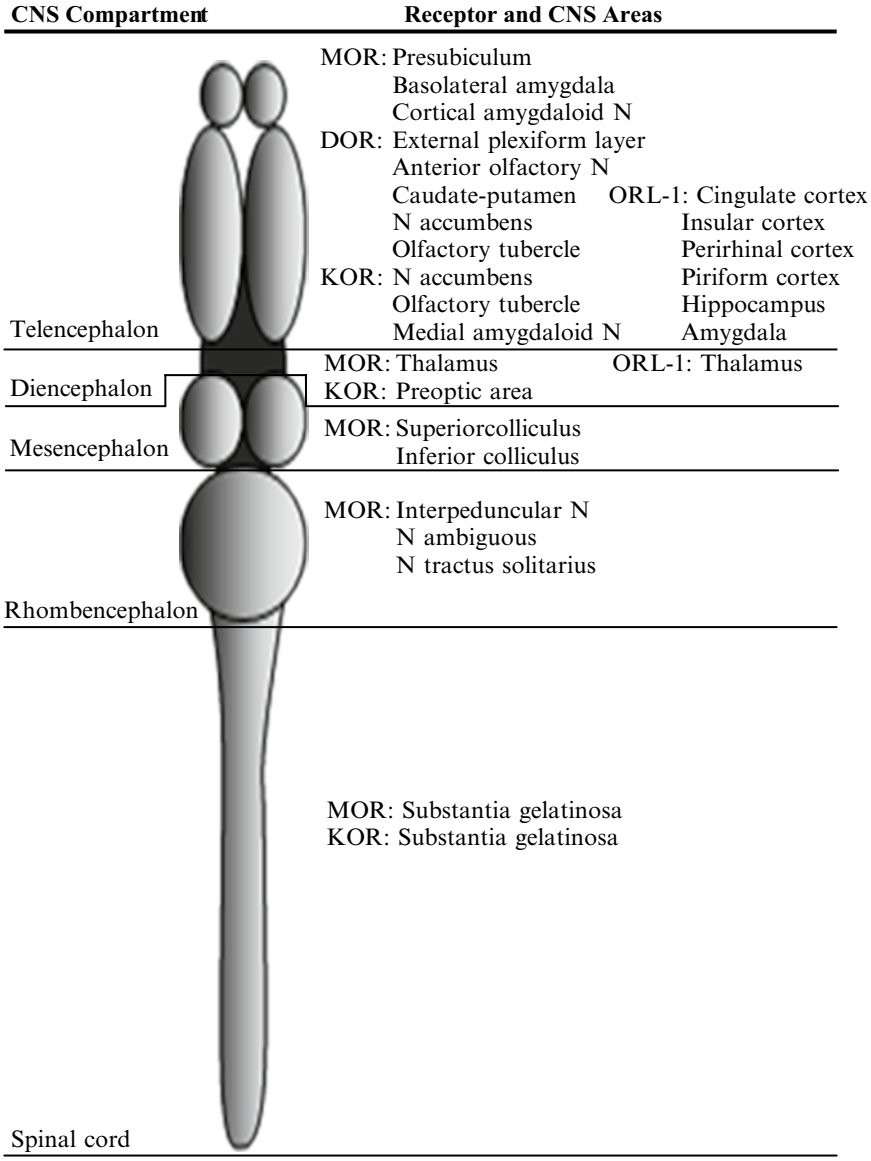

Fig. 66.2 Distribution of opioid receptors in the mammalian CNS. CNS areas with very high density of receptor binding (Region data from Mansour et al. 1995; Sim-Selley et al. 2003; Yaster et al. 2003)

Table 66.3 Selective ligands for opioid receptors

Function	MOR	DOR	KOP	ORL
Agonist	DAMGO	DPDPE	U50,488H	Nociceptin
	Endomorphin-1	SNC 80	U69595	
	Endomorphin-2			
Antagonist	CTAP	Naltrindole	Nor-binaltorphimine	(Unknown)

A variety of ligands have been developed that, unlike endogenous opioids, bind selectively to specific opioid receptors. These compounds play a key role in identifying opioid receptors that are selectively involved during specific behavioral processes

Stevens 2009). Although the amino acid sequences of opioid receptors are very similar across species and within species, nonmammalian opioid receptors are more similar to each other than are mammalian opioid receptors (Stevens et al. 2007).

In mammals, endogenous opioid peptides bind differentially, but not exclusively, to each opioid receptor. The exception is the ORL-1 receptor, which does not bind endogenous opioids. For instance, β-endorphin and enkephalins have a higher affinity for the MOR and the DOR, than for the KOR. In turn, dynorphins bind preferentially to the KOR and nociceptin binds to the ORL-1 receptor. Finally, endomorphin-1 and endomorphin-2 bind specifically to the MOR. In addition to these endogenous opioids, a number of receptor-selective ligands have been developed (Table 66.3).

66.3 Opioid Receptors and Absolute Incentive Value

One strategy used to clarify the role of the opioid system in behavior has been to study the opioid effects in combination with the stimulation of specific brain areas. Following this rationale, it has been proposed that opioid receptors located in the hindbrain may be involved in sensory and metabolic functions, opioid receptors located in the amygdala may regulate the hedonic (i.e., appetitive or aversive) properties of food, and opioid receptors in the hypothalamus may control energetic needs. In addition, opioid receptors located in the basal ganglia may be involved in the modulation of motor patterns (Aubert et al. 2007). This section emphasizes opioid modulation of food incentives.

The role of the opioid system on taste palatability was suggested by the reduction of drinking behavior in animals exposed to solutions of saccharine, sucrose, saline, and hydrochloric acid while under the influence of the nonselective opioid antagonist naloxone (Levine et al. 1982). Similar results were reported using sweetened or unsweetened food and manipulating the food deprivation states. Levine et al. (1995) found that naloxone reduced consumption of sweet food, when compared to unsweetened food, independently of the type of deprivation. In addition, naloxone reduced sucrose preference in two-bottle tests (sucrose vs. water) for wild-type and β-endorphin knockout mice, but it had no effect on enkephalin and dynorphin knock-out strains (Hayward et al. 2006). Naloxone blockage of opioid receptors seems to devalue the palatability of sucrose solutions, rather than the postingestional effects of sucrose. This is suggested by two series of experiments using naloxone-induced suppression of sucrose in a preparation of feeding by open gastric fistula. In the first series of experiments, naloxone reduced sucrose consumption on rats exposed to sham drinking (Rockwood and Reid 1982). In the second series of experiments, naloxone reduced sucrose intake in rats exposed to 10% and 20% sucrose to a level similar to that of saline controls exposed to 5% and 10% sucrose (Kirkham and Cooper 1988).

Following an incentive-motivation framework, Berridge (2004) suggested a distinction between "liking" and "wanting." Liking is defined as the hedonic reaction triggered by the immediate presentation

of a reward, whereas wanting refers to the incentive significance of the reward. This distinction is consistent with Craig's (1918) classification of behavior in terms of consummatory (i.e., liking) and appetitive components (i.e., wanting), and it was proposed to reconcile the effects of some physiological manipulations on behavior supported by access to incentives. For example, dopamine antagonists that disrupt the effects of the mesolimbic dopaminergic system reduce wanting, thus decreasing motivation to seek incentives. However, when incentives are delivered passively (e.g., intraoral sucrose infusions), animals show normal liking responses (e.g., lip licking, tongue protrusion). Conversely, naloxone blockage of opioid receptors in key areas of the reward system (e.g., nucleus accumbens, ventral pallidum) eliminates orofacial liking responses, whereas microinjections of endogenenous opioids increase them.

Endogenous opioid and cannabinoid mechanisms in the nucleus accumbens are critical for the orofacial responses to sweetness used as an index of liking (i.e., consummatory-like responses; Berridge 2004). Administration of DAMGO (a selective MOR agonist) in the medial accumbens shell increases these orofacial liking responses (Peciña and Berridge 2005). Additional studies with opioids shed light on the functional connection between the nucleus accumbens and the posterior ventral pallidum. For example, the enhancing effects of DAMGO administered in the posterior ventral pallidum on liking responses were blocked by microinjections of naloxone in the nucleus accumbens. Moreover, opioid activation in any of the two areas causes an increase in Fos protein expression in the other area, an effect suppressed by naloxone (Smith et al. 2009). Thus, opioid release in the nucleus accumbens, amygdala, and ventral pallidum are intimately involved in incentive palatability.

66.4 Opioid Receptors and Relative Incentive Value

Incentive relativity involves a comparison process, usually between present and remembered incentives. Behavioral preparations used to study incentive relativity typically involve some type of unexpected reward devaluation or reduction that triggers the comparison (Flaherty 1996). The role of the opioid system in incentive relativity has been studied in several preparations (Table 66.4; Papini 2009).

Table 66.4 Effects of opioid manipulations on incentive relativity

Preparation	Drugs	Dose	Administered	Reference
cSNC	Morphine	0.5–16.0 mg/kg	Pretrial	Rowan and Flaherty (1987)
	DPDPE	24 μg/kg	Pretrial	Wood et al. (2005)
	DPDPE	24 μg/kg	Post-trial	Daniel et al. (2009)
	U50,488H	1–10 mg/kg	Pretrial	Wood et al. (2008)
	U50,488H	1–3 mg/kg	Post-trial	Wood et al. (2008)
	Naloxone	0.25–1.0 mg/kg	Pretrial	Rowan and Flaherty (1987)
	Naloxone	2 mg/kg	Pretrial	Pellegrini et al. (2005)
	Naloxone	2 mg/kg	Post-trial	Daniel et al. (2009)
	Naltrindole	1 mg/kg	Pretrial	Pellegrini et al. (2005)
	Naltrindole	1 mg/kg	Post-trial	Daniel et al. (2009)
iSNC	FK33–824	0.3 mg/kg	Pretrial	Lynch and Clark (1983)
	Naloxone	1–10 mg/kg	Pretrial	Lynch and Clark (1983)
cE	Naloxone	2 mg/kg	Pretrial	Norris et al. (2008)
iE	Naloxone	2 mg/kg	Pretrial	Norris et al. (2009)
pE	Naloxone	2 mg/kg	Post-trial	Daniel et al. (2009)
EFF	Naloxone	2 mg/kg	Pretrial	Norris et al. (2009)

This table summarizes research on the effects of opioid drugs on situations involving unexpected incentive devaluations. Opioid administration was intraperitoneal, except in Lynch and Clark (1983), who used subcutaneous administration

Most of the information originates in the consummatory successive negative contrast (cSNC) situation, in which the consummatory behavior of a group exposed to a downshift in sucrose concentration (e.g., from 32% to 4% sucrose) is compared to that of an unshifted control group only exposed to the lower concentration (e.g., 4% sucrose). The incentive downshift leads to a sharp and transient suppression of consummatory behavior and opioid drugs modulate the degree of suppression. The use of an unshifted control allows an assessment of the extent to which opioids effects are selective to the incentive downshift experience. For example, morphine attenuated consummatory suppression (i.e., attenuated cSNC), whether administered before the first or before the second downshift trial (Rowan and Flaherty 1987). Naloxone reversed the effects of morphine (Rowan and Flaherty 1987) and also enhanced cSNC (Pellegrini et al. 2005). Except for the highest morphine dose (16 mg/kg), neither morphine nor naloxone affected the consummatory behavior of unshifted controls, suggesting that the effect was selective to the downshift experience and therefore unrelated to potential opioid effects on motor, sensory, or palatability aspects of the task. Naloxone acts by distorting the normal process of detection of the incentive downshift, which involves a ratio comparison between pre- and postshift sucrose concentrations (Papini and Pellegrini 2006). Opioid blockage shifts the incentive comparison from a ratio to an absolute difference comparison (Daniel et al. 2009). However, neither naloxone nor naltrindole (selective DOR antagonist) affects the course of cSNC when administered immediately after the first downshift trial.

Naloxone also leads to similar results in other training situations. For example, naloxone increases behavioral suppression in the iSNC situation (Lynch and Clark 1983), facilitates instrumental extinction of lever-press responses acquired by pairings with food or sucrose pellets (Norris et al. 2009), and promotes consummatory extinction of licking responses paired with sucrose solutions (Norris et al. 2008). Naloxone also eliminates the escape-from-frustration effect in which rats exposed to appetitive extinction have the opportunity to "escape" to a neutral compartment by jumping over a barrier (Norris et al. 2009). However, as in the cSNC situation, posttrial naloxone administration during appetitive extinction leads to no detectable effects on lever-press responses (Daniel et al. 2009). All together, these results suggest that: (1) opioid receptors are normally engaged during exposure to incentive downshifts; (2) their role is to attenuate the emotional impact of the downshift; and (3) they probably play no direct role in the consolidation of the emotional memory of the downshift event.

Opioid modulation of cSNC is also quite selective with respect to the amount of downshift experience. For example, the DOR agonist DPDPE reduces cSNC on the first downshift trial, but has no effect on the second downshift trial (Wood et al. 2005). Similarly, the DOR antagonist naltrindole enhances cSNC selectively on the first downshift trial (Pellegrini et al. 2005). Thus DORs are engaged during the initial response to the incentive downshift, but are less relevant as the animal learns about the situation with more extended practice. Interestingly, the KOR agonist U50,488H has the opposite profile. It attenuates cSNC when administered on the second downshift trial, but has no effect when administered on the first downshift trial (Wood et al. 2008). Because both morphine (Rowan and Flaherty 1987) and naloxone (Pellegrini et al. 2005) influence cSNC on both the first and second downshift trials, and because these drugs have greater affinity for the MOR, it is tempting to conclude that the MOR is not trial selective in the cSNC situation. The picture emerging from these results is that different combinations of opioid receptors are engaged as a function of the amount of experience with the downshifted incentive. A MOR–DOR combination is active during the early stages of downshift detection, whereas a MOR–KOR combination becomes active as the animal interacts further with the downshifted solution. Such combinations await further research with selective MOR opioids, but it is intuitively consistent with heterodimerization of MOR–DOR complexes. MOR–DOR heterodimers have been postulated to underlie enhanced hypoalgesia after spinal cord administration of morphine (Gomes et al. 2004; Snook et al. 2008).

66.5 Applications to Areas of Health and Disease

The experiments reviewed in the previous section demonstrate that endogenous opioids are normally activated by an episode of incentive downshift. Thus, further activation by opioid agonists (e.g., morphine, DPDPE, U50,488H) reduced cSNC, whereas interference by antagonists (e.g., naloxone, naltrindole) enhanced cSNC. But, like most behavioral phenomena, recovery from incentive downshift is a variable process, with individuals exhibiting behavioral phenotypes ranging from very fast recovery (i.e., normal consummatory levels after a single exposure to the downshifted solution) to very slow recovery (i.e., little or no evidence of recovery after five trials, the usual length of the postshift phase in cSNC experiments). Even rats that show very similar consummatory suppression on the first downshift trial can differ dramatically in the speed of recovery from cSNC (Pellegrini et al. 2005). Interestingly, if these individual differences in recovery were related to differences in some property of the opioid system, one would predict a direct correspondence between recovery from reward downshift and general sensitivity to opioid treatments.

MORs are known to exhibit allelic variation in rodents and humans (e.g., Mayer and Höllt 2001; Zimprich et al. 1995). MORs are important for health-related reasons because they are one site of action for morphine and naloxone, two drugs with extensive clinical applications. Allelic variations differ in the efficacy with which the MOR interacts with opioid agonists and have clinical implications for addiction and pain treatments (Drews and Zimmer 2010; Klepstad 2007). Thus, if individual differences in opioid receptor efficacy and recovery from cSNC are related, then slow recovery animals should differ from fast recovery animals in terms of sensitivity to opioid blockage. Consistent with this hypothesis, rats that recovered more slowly from incentive downshift exhibited greater sensitivity to naloxone treatment in an activity test than rats that recovered faster (Pellegrini et al. 2005). Slow- and fast-recovery animals did not differ in their level of suppression during the first downshift trial, as well as in terms of growth rates or water intake. However, siblings were significantly more likely than chance to be assigned to the same recovery group.

The opioid system (receptors and endogenous neuropeptides) participates in a wide variety of behaviorally relevant processes. The role of this neurochemical system in nutrition relates to its ability to modulate incentive value, both absolute and relative. As a result of this incentive function, it is not surprising that the area of influence of opioid modulation extends beyond that of food reinforcement processes. For example, in addition to the well-established role in pain and analgesia, opioids participate in fear conditioning, social stress, drug tolerance and drug dependence, drug abuse, gastrointestinal function, and mental disorders among others (Bodnar in press).

Summary Points

- Opioid receptors and endogenous peptides play a role in a wide variety of behavioral and physiological processes.
- Four types of opioid receptors have been identified: mu (MOR), delta (DOR), kappa (KOP), and opioid-receptor-like receptor (ORL-1).
- A variety of endogenous opioids have been identified, including β-endorphin, met-enkephalin, dynorphins, and nociceptin, among others.
- Several receptor-selective compounds are available for research (e.g., DAMGO, DPDPE, and U50,488H selectively agonize MOR, DOR, and KOR, respectively).
- Opioid receptors and neuropeptides modulate the absolute (palatability) and relative (incentive contrast) value of incentives.

- Incentive value refers to the hedonic dimension of stimuli such as food and fluids, that is, to their appetitive or aversive value.
- Opioid peptides and receptors modulate food palatability and so-called liking orofacial responses.
- Endogenous opioids are released during events involving unexpected incentive devaluations.
- Different opioid receptors affect behavior at different points in the process of adjustment to incentive devaluation.

Key Terms

Endogenous opioids: Gene products expressed in the vertebrate CNS, acting on membrane receptors to modulate synaptic transmission.
Opioid receptors: Gene products of the G-protein-coupled type, expressed in the vertebrate CNS, sensitive to a variety of endogenous and exogenous opioid peptides, and modulating synaptic transmission.
Absolute incentive value: The direct hedonic (i.e., appetitive–aversive) dimension of environmental resources such as food and fluids.
Relative incentive value: The hedonic value of a current incentive in relation to the incentive expected on the basis of prior experience.
Negative incentive contrast: Greater rejection of a small incentive in animals previously exposed to a large incentive, relative to animal always exposed to the small incentive.

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