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Delta opioid receptors in brain function and diseases

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ABSTRACT

Evidence that the delta opioid receptor (DOR) is an attractive target for the treatment of brain disorders has strengthened in recent years. This receptor is broadly expressed in the brain, binds endogenous opioid peptides, and shows as functional profile highly distinct from those of mu and kappa opioid receptors. Our knowledge of DOR function has enormously progressed from in vivo studies using pharmacological tools and genetic approaches. The important role of this receptor in reducing chronic pain has been extensively overviewed; therefore this review focuses on facets of delta receptor activity relevant to psychiatric and other neurological disorders. Beneficial effects of DOR agonists are now well established in the context of emotional responses and mood disorders. DOR activation also regulates drug reward, inhibitory controls and learning processes, but whether delta compounds may represent useful drugs in the treatment of drug abuse remains open. Epileptogenic and locomotor-stimulating effects of delta agonists appear drug-dependent, and the possibility of biased agonism at DOR for these effects is worthwhile further investigations to increase benefit/risk ratio of delta therapies. Neuroprotective effects of DOR activity represent a forthcoming research area. Future developments in DOR research will benefit from in-depth investigations of DOR function at cellular and circuit levels.

Contents

1. Introduction

Mu, delta and kappa opioid receptors are G protein coupled receptors, which play a central role in pain control, and are key players in hedonic homeostasis, mood and well-being. The three receptors and their endogenous opioid peptides also regulate responses to stress, and a number of peripheral physiological functions including respiratory, gastrointestinal, endocrine and immune processes. Opioid receptors are highly homologous in sequence, and their crystal structure has been recently elucidated at high-resolution by X-Ray crystallography (Granier et al., 2012; Manglik et al., 2012; Wu et al., 2012). All three receptors

Abbreviations: Amy, amygdala; CA, continuous access; CeA, central nucleus of the amygdala; Cg, cingulate cortex; CPA, conditioned place aversion; CPP, conditioned place preference; CPu, caudate putamen nucleus; Cx, cortex; DOR, delta opioid receptor; EEG, electroencephalography; Enk, enkephalin; FCx, frontal cortex; GPCR, G protein coupled receptor; Hipp, hippocampus; Hyp, hypothalamus; i.c.v., intracerebroventricular; i.p., intraperitoneal; i.v., intravenous; IA, intermittent access; KO, knockout; Nacc, nucleus accumbens; NTI, naltrindole; OB, olfactory bulb; p.o., pers os; PR, progressive ratio; PVN, paraventricular nucleus; RS, retrosplenial cortex; s.c., subcutaneous; SA, self-administration; SC, spinal cord; Th, thalamus; VTA, ventral tegmental area.

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inhibit neuronal activity, via reduced neuronal firing or lower transmitter release, and a main goal in opioid research is the identification of receptor-mediated signaling pathways that operate in vivo, to regulate physiology and behavior (Pradhan et al., 2012).

In the past two decades, refinement of pharmacological tools and availability of genetic approaches have clarified the specific role of each opioid receptor in many aspects of opioid-related responses (Shippenberg et al., 2008; Gianoulakis, 2009; Sauriyal et al., 2011; Lutz & Kieffer, in press; Gaveriaux-Ruff, in press). Mu opioid receptors mediate both analgesic and addictive properties of clinically useful and abused opiates. Mu opioid receptor activation strongly inhibits severe pain, and is a major target for post-operative and cancer pain management (Zollner & Stein, 2007). Mu receptors are also central for reward processing (Le Merrer et al., 2009), representing a main factor in the initiation of addictive behaviors. Kappa opioid receptors also release pain (Chavkin, 2011) but oppose mu receptors in the regulation of hedonic homeostasis. The notion that kappa receptor blockade alleviates stress responses and depressive states is raising increasing interest (Shippenberg, 2009; Knoll & Carlezon, 2010).

Delta opioid receptors (also known as δ receptors, DORs or DOP receptors in the IUPHAR nomenclature) have emerged as an attractive target in many respects. In accordance with the rodent mRNA distribution, DOR in the human central nervous system is expressed in cortical regions and limbic structures such as hippocampus and amygdala, as well as basal ganglia and hypothalamus (Simonin et al., 1994; Peckys & Landwehrmeyer, 1999; Smith et al., 1999; Peng et al., 2012).

The development of highly selective delta opioid agonists and rapid progress in mouse mutagenesis approaches targeting the *Oprd1* gene (Filliol et al., 2000; Scherrer et al., 2006, 2009; Gaveriaux-Ruff et al., 2011) have set delta receptors as a model system for the analysis of G protein coupled receptor (GPCR) trafficking and biased signaling in vivo, and established this receptor as a promising target to treat chronic pain and mood disorders (Pradhan et al., 2011). The stimulation of delta opioid receptors strongly reduces pain, specifically under situations of persistent pain, and mechanisms of delta agonist analgesia have been extensively overviewed recently (Gaveriaux-Ruff & Kieffer, 2011). Here we will focus on non-nociceptive facets of delta receptor function, and summarize accumulating preclinical data supporting the key role of delta receptors in emotional processes (Tables 1 and 2), drug reward and addiction (Table 3), and other aspects of potential therapeutic relevance (Table 4). Both genetic approaches and behavioral pharmacology concur to support an implication of delta receptors in psychiatric and neurological disorders, and delta agonists have entered clinical trials (Table 5).

2. Delta opioid receptor and the control of emotional processes

Genetic studies have revealed a prominent role for DORs in emotional processing more than a decade ago. Knockout of the *Oprd1* gene, encoding DOR, led to higher anxiety-related responses and depressive-like behaviors (Filliol et al., 2000). This activity was clearly DOR-selective, since neither mu receptor knockout mice nor kappa receptor knockout mice showed a similar phenotype (Filliol et al., 2000). Mice deficient for *Penk* gene, encoding the pre-proenkephalin precursor, also showed increased levels of anxiety using a large number of experimental testing conditions (Konig et al., 1996; Ragnauth et al., 2001), suggesting that DOR/enkephalinergic systems exert control over anxiety-related behaviors. This was later supported by experiments performed in wild-type and mu receptor mutant mice, which both showed similar decreased levels of anxiety upon systemic administration of RB101, an enkephalinase inhibitor (Mas Nieto et al., 2005). Interestingly, over-expression of enkephalin by a virus approach in the amygdala potentiates the anxiolytic effect of benzodiazepines and this effect is abolished by systemic naltrindole (NTI)

Table 1
Delta opioid receptor function in anxiety-related behavior control.

Approach	Model/compound	Test	Delta compound administration (route/dose)	Anxiety level (vs control)	References
Genetic					
	DOR KO mice	Elevated plus maze		↑	Filliol et al., 2000
		Light-dark box		↑	Filliol et al., 2000
		Open field		↔	Filliol et al., 2000
	Enk KO mice	Open field		↑	Konig et al., 1996; Ragnauth et al., 2001
		Elevated O-maze		↑	Konig et al., 1996
		Resident-intruder test		↑	Konig et al., 1996
		Light-dark box		↑	Ragnauth et al., 2001
		Fear conditioning		↑	Ragnauth et al., 2001
DOR antagonist	Rats/NTI	Elevated plus maze	s.c. (1, 3 or 5 mg/kg)	↑	Saitoh et al., 2004; Saitoh et al., 2005; Perrine et al., 2006
		Elevated plus maze	Local into Hipp (0.5, 1 or 2 μg/rat)	↑	Solati et al., 2010
		Light-dark box	Local into BLA (10 pmol/rat)	↑	Narita et al., 2006a
	Mice/NTI	Light-dark box	i.c.v. (1 nmol/mouse)	↑	Narita et al., 2006a
		Light-dark box	s.c. (1 mg/kg)	↑	Narita et al., 2006b
		Light-dark box	Local into cingulate Cx (1 pmol/mouse)	↑	Narita et al., 2006b
		Elevated plus maze	s.c. (1 mg/kg)	↑	Narita et al., 2006b
		Elevated plus maze	Local into cingulate Cx (1 pmol/mouse)	↑	Narita et al., 2006b
DOR agonist	Rats/SNC80	Fear conditioning	s.c. (1 or 3 mg/kg)	↓	Saitoh et al., 2004
		Elevated plus maze	s.c. (1-20 mg/kg)	↓	Saitoh et al., 2004; Perrine et al., 2006
		Open field	s.c. (1 or 3 mg/kg)	↔	Saitoh et al., 2004
		Defensive burying paradigm	s.c. (5 mg/kg)	↓	Perrine et al., 2006
		Elevated O-maze	s.c. (5 mg/kg)	↓	Ambrose-Lanci et al., 2008
	Rats/DPDPE	Elevated plus maze	Local into CeA (0.5 or 1.5 μg/μl; 1 μl/CeA)	↓	Randall-Thompson et al., 2010
	Mice/UFP-512	Light-dark box	i.p. (1 mg/kg)	↓	Vergura et al., 2008
		Elevated plus maze	i.p. (0.1 or 1 mg/kg)	↓	Vergura et al., 2008
		Open Field	i.p. (0.1 or 1 mg/kg)	↔	Vergura et al., 2008
	Rat/enkephalin	Elevated plus maze	Local into Hipp (1, 2 or 5 μg/rat)	↓	Solati et al., 2010
	Mice/RB101	Elevated O-maze	i.p. (80 mg/kg)	↓	Mas Nieto et al., 2005
	Rats/opiorphin	Defensive burying paradigm	i.v. (1 mg/kg)	↔	Javelot et al., 2010
	Rats/AZD2327	Modified Geller-Seifter conflict test	p.o. (0.5, 1 or 5 mg/kg)	↓	Hudzik et al., 2011