Progress in Neuropsychopharmacology & Biological Psychiatry 86 (2018) 301–312

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Zebrafish models relevant to studying central opioid and endocannabinoid systems

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ARTICLE INFO

Keywords:
Opioid system
Endocannabinoid system
Zebrafish
High-throughput screening

ABSTRACT

The endocannabinoid and opioid systems are two interplaying neurotransmitter systems that modulate drug abuse, anxiety, pain, cognition, neurogenesis and immune activity. Although they are involved in such critical functions, our understanding of endocannabinoid and opioid physiology remains limited, necessitating further studies, novel models and new model organisms in this field. Zebrafish (*Danio rerio*) is rapidly emerging as one of the most effective translational models in neuroscience and biological psychiatry. Due to their high physiological and genetic homology to humans, zebrafish may be effectively used to study the endocannabinoid and opioid systems. Here, we discuss current models used to target the endocannabinoid and opioid systems in zebrafish, and their potential use in future translational research and high-throughput drug screening. Emphasizing the high degree of conservation of the endocannabinoid and opioid systems in zebrafish and mammals, we suggest zebrafish as an excellent model organism to study these systems and to search for the new drugs and therapies targeting their evolutionarily conserved mechanisms.

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https://doi.org/10.1016/j.pnpbp.2018.03.024
Received 23 January 2018; Received in revised form 26 March 2018; Accepted 26 March 2018
Available online 28 March 2018

Table 1
Summary of physiological effects of main ligands for opioid and cannabinoid receptors, based on clinical and experimental (rodent) models.

Effect	Ligands	Mechanism of action	References
Anti-nociception	Morphine, methadone	Binding to MOP activates descendent inhibitory serotoninergic neurons and produces analgesia	(Ghelardini et al., 2015)
	WIN-55, 212-2	CB1R activation suppresses the nociceptive sensitization	(Elikottil et al., 2009)
Hypothermia	U-50, 488H	KOP activation	(Rawls and Benamar, 2011)
	Deltorphin-II	DOP activation	
	AEA, NADA	Activation of TRPV1 channels causes vasodilation	(Elphick and Egertova, 2001)
Reward	Morphine, methadone, DALDA, DAMGO	Systemic MOP and DOP agonists produce positive reinforcement KOP agonists induce aversion, hallucinations, and malaise	(Fattore et al., 2005)
	WIN-55,212-2	Inhibition of CB1R prevents opioid-evoked reward and some other pharmacological effects	(Fattore et al., 2005)
Memory	WIN-55,212-2	Selective CB1R agonists disrupt hippocampus-dependent learning. WIN-55,212-2 attenuates spatial memory loss, reduces activated microglia and modulates neurogenesis	(Hampson and Deadwyler, 1999) (Bilkei-Gorzo, 2012)
	Rimonabant	CB antagonism causes hyperalgesia and improves memory	(Grotenhermen, 2003)
Sleep	Methadone, morphine	MOP agonists inhibit REM sleep, while DOP and KOP agonists have no effect	(Ling and Pasternak, 1982)
Aggression	ACEA	CB1R agonist, acutely reduces mouse aggression	(Rodriguez-Arias et al., 2013)
Antitusive effect	DAMGO, U-50,488H	Selective MOP and highly selective KOP agonists, but not a DOP agonist, exert antitussive effects	(Kamei, 1998)
Diuresis	Bremazocine, U-50,488	KOP agonists, but not MOP and DOP agonists, suppress vasopressin levels	(Leander et al., 1985)
Inhibition of intestinal motility	DALDA, DAMGO, DPDPE	Motility is blocked by MOP and DOP, but not KOP, agonists	(Holzer, 2009)
	AEA, 2-AG	Reduced motility via CB1R, but not CB2R activation	(Aviello et al., 2008)
Emesis	Morphine, methadone	Low doses of MOP agonists stimulate, and higher doses may suppress, vomiting	(Sobczak et al., 2014)
	Dronabinol, nabilone	Oral cannabinoids reduce nausea and vomiting	(Badowski, 2017)
Immune activity	Morphine	Chronic opioids decrease proliferative capacity of macrophage progenitor cells and lymphocytes	(Roy and Loh, 1996)
	THC	Cannabis consumption alters susceptibility to viral infections and dysregulates cytokines	(Greineisen and Turner, 2010)
Modulation of anxiety	SNC-80	DOP agonist evokes dose-dependent anxiolysis	(Perrine et al., 2006)
	Naltrindole	DOP antagonist evokes anxiety-like states in rats	
	Anandamide, 2-AG	Low doses reduce, and high doses increase, anxiety. CB1R antagonism is anxiogenic and impairs the extinction of aversive memories	(Moreira and Wotjak, 2010)
Locomotion	Morphine	Dose-dependent stereotypic hyperactivity	(Mickley et al., 1990)
	THC, WIN-55,212-2, CP-55,940	Agonists induce biphasic effects (hyperactivity at low and motor deficits at higher doses)	(Rodriguez-Arias et al., 2013)
Feeding	DALDA, DAMGO	Hyperphagia elicited by MOP agonists in a subset of NAcc neurons	(Katsuura and Taha, 2010)
	AEA	CB1R-mediated stimulation of appetite and feeding	(Kirkham, 2005)
Neurogenesis	THC	Activation of CB1R is required for the axonal growth	(Williams et al., 2003)
	AEA	Modulation of neural progenitor cell proliferation	(Aguado et al., 2005)

Abbreviations: 2-AG - 2-Arachidonoylglycerol; ACEA - Arachidonyl-2-chloroethylamide; AEA – Anandamide (*N*-arachidonoylethanolamine); CB1R – Cannabinoid receptor 1; CB2R – Cannabinoid receptor 2; CP-55,940 - 2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropyl) cyclohexyl]-5-(2-methyloctan-2-yl)phenol; DALDA - H-Tyr-D-Arg-Phe-Lys-NH2; DAMGO - H-Tyr-D-Ala-Gly-*N*-MePhe-Gly-OH; DOP - delta-opioid receptor; DPDPE - H-Tyr-D-Pen(1)-Gly-Phe-D-Pen(1)-OH; KOP - kappa-opioid receptor; MOP - mu-opioid receptors; NADA - N-Arachidonoyl dopamine; REM – Rapid eye movement; SNC-80 - (+)-4-[(αR)-α-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide; THC - (−)-trans-Δ^9-tetrahydrocannabinol; TRPV1 - Transient receptor potential cation channel subfamily V member 1; U-50,488H - trans-3,4-dichloro-*N*-methyl-*N*-[2-(1 -pyrrolidinyl)-cyclohexyl]-benzeneacetamide; WIN-55,212-2 - (2,3-dihydro-5-methyl-3-((4-morpholinyl)methyl)pyrrolo-(1,2,3-de)-1,4-benzoxazin-6-yl)(1-naphthalenyl)methanone monomethanesulfonate.

1. Introduction

1.1. Central opioid and endocannabinoid systems

Opioids are hypnotic and analgesic drugs (Tables 1 and 2) acting through central mu-, delta- and kappa-opioid receptors (MOP, DOP and KOP) (Ballantyne and Sullivan, 2017) encoded in humans by their respective genes *OPRM1*, *OPRD1* and *OPRK1* (Table 3). Met- and Leu-enkephalin were the first reported endogenous ligands for these receptors, followed by the discovery of other opioids (enkephalins, dynorphins and beta-endorphin) produced by proteolytic cleavage of large protein precursors preproenkephalin (PENK), preprodynorphin (PDYN), proorphanin/prepronociceptin (PNOC) and proopiomelanocortin (POMC). Opioid peptides share a common N-terminal Tyr-Gly-Gly-Phe sequence that binds to their receptors (Le Merrer et al., 2009). Additionally, a novel member of the opioid receptor family (NOP) (Pathan and Williams, 2012) was identified to bind nociceptin, an endogenous opioid devoid of the enkephalin sequence at its N-terminus and, thus, exerting a potent anti-analgesic action insensitive to naloxone (Mogil and Pasternak, 2001).

Opioid peptides and their receptors are widely expressed throughout the brain reward circuits. In general, MOP and (to a lesser extent) DOP agonists produce reward, whereas KOP agonists evoke aversion, hallucinations and malaise (Table 1). Conversely, MOP and DOP antagonists suppress reward properties of various agents, whereas KOP antagonists facilitate these effects (Le Merrer et al., 2009). Since opioids are also well recognized as analgesic drugs (Table 1), finding pathway-specific opiate agonists that can activate antinociceptive signaling without causing MOP-mediated euphoria or KOP-mediated dysphoria, becomes important clinically (Al-Hasani and Bruchas, 2011). However, despite the introduction of potent synthetic opioid agonists (e.g., methadone and fentanyl), and the discovery of endogenous opioid peptides, developing novel safe analgesics remains problematic (Manglik et al., 2016). Recent studies suggest that opioid-induced analgesia results from MOP signaling through the activation of $G_{i/o}$ –proteins (Al-Hasani and Bruchas, 2011), while many side-effects, including respiratory depression, involve the β-arrestin pathway downstream of MOP (Manglik et al., 2016).

Discovered recently, the endocannabinoid system broadly modulates both excitatory and inhibitory neuronal circuits via widely distributed cannabinoid receptors CB1R and CB2R (Morena et al., 2016). The endocannabinoid system regulates various physiological functions (Table 1), also potently modulating synaptic neurotransmission (Klein et al., 2001). In general, the endocannabinoid system is composed of