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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Alleviating pain with delta opioid receptor agonists: evidence from experimental models

Sophie Berthiaume[1] · Khaled Abdallah[1] · Véronique Blais[1] · Louis Gendron[1]

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Abstract
The use of opioids for the relief of pain and headache disorders has been studied for years. Nowadays, particularly because of its ability to produce analgesia in various pain models, delta opioid receptor (DOPr) emerges as a promising target for the development of new pain therapies. Indeed, their potential to avoid the unwanted effects commonly observed with clinically used opioids acting at the mu opioid receptor (MOPr) suggests that DOPr agonists could be a therapeutic option. In this review, we discuss the use of opioids in the management of pain in addition to describing the evidence of the analgesic potency of DOPr agonists in animal models.

Keywords Delta opioid receptor · Pain · Primary afferents · G protein-coupled receptors · Trafficking

Introduction

Opioids are extensively used for the treatment of moderate to severe pain. Opioid compounds, as well as endogenous opioid peptides, produce their effects on neurotransmission through the activation of opioid receptors (Bodnar 2019). There are three different opioid receptors named mu (MOPr), delta (DOPr) and kappa (KOPr) (Kieffer and Gaveriaux-Ruff 2002). While the MOPr is the major target of commonly used opioids, its activation by morphine or other opioids induces important adverse effects (Al-Hasani and Bruchas 2011; McQuay 1999). In this review, we briefly describe the major pain pathways and the distribution of DOPr along those pathways. Finally, an overview of the analgesic effects of DOPr agonists in different preclinical models is provided, together with the conclusion of clinical trials investigating the role of DOPr agonists for pain.

✉ Louis Gendron
Louis.Gendron@USherbrooke.ca

[1] Département de Pharmacologie-Physiologie, Institut de Pharmacologie de Sherbrooke, Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke, Faculté de médecine et des sciences de la santé, Université de Sherbrooke, 3001, 12th Avenue North, Sherbrooke, QC J1H 5N4, Canada

Pain

The International Association for the Study of Pain (IASP) qualifies pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is a complex and subjective process experienced at an individual level. Nowadays, numerous medications such as NSAID (Non-Steroidal Anti-Inflammatory Drugs) and opioids are used to alleviate acute and chronic pain. Despite their important analgesic potency, opioids are not always well tolerated by their users and often not suitable for a given pain condition. A combination of analgesics is sometimes required, further exacerbating unwanted effects (McQuay 1999). Most opioids currently used in the clinic bind MOPr (Smith and Peppin 2014). However, the activation of this receptor is also responsible for the common unwanted effects associated with opioids. Indeed, the most important adverse effects of opioids are constipation, tolerance, addiction, respiratory depression and sedation (Bailey and Connor 2005). Those effects are particularly debilitating and therefore restrain the usefulness of MOPr agonists under chronic pain conditions. On the other hand, DOPr agonists produce antinociception with less unwanted effects than the currently used opioids (Bodnar 2019; Gaveriaux-Ruff and Kieffer 2011; Gendron et al. 2015). Most importantly, it is generally accepted that DOPr agonists do not produce abuse potential (Negus et al. 1998).

Pain pathways

Pain transmission involves two major pathways (for reviews see Basbaum et al. 2009 and Yam et al. 2018). The first, known as the ascending pain pathway, is characterized by a neuronal circuit capable of integrating signals generated by a wide variety of noxious stimuli. More specifically, the ascending pathway is activated when stimuli from thermal, mechanical or chemical sources activate a first-order neuron known as nociceptor. Activated nociceptors relay the noxious signals to the spinal cord by releasing excitatory neurotransmitters on second-order neurons. The latter, called projection neurons, are then activated and transmit the information to the thalamus which in turn signals to the somatosensory cortex, the insula, and the cingulate cortex.

The second pathway implicated in pain processing is the descending pain pathway. This pathway is known to play a modulatory role. Indeed, a phenomenon best known as "diffuse noxious inhibitory controls" (DNIC) previously described by Le Bars plays a major role in the modulation of pain (Le Bars et al. 1992). DNIC, now termed conditioned-pain modulation (CPM) in human, involves specific supraspinal structures such as subnucleus reticularis dorsalis (SRD) (Le Bars et al. 1992). Besides SRD, other structures in the CNS such as the hypothalamus, the amygdala, the periaqueductal gray (PAG) and the rostro-ventral medulla (RVM) play a role in the modulation of noxious stimuli through their projections to the spinal cord. Interestingly, all three opioid receptors (MOPr, DOPr and KOPr) and their endogenous peptides are present at different levels along these pain pathways where they can participate in the modulation of pain (Al-Hasani and Bruchas 2011).

Another important pain circuit is the trigeminal pain pathway (Bicanic et al. 2019). The trigeminal system innervates the head and is therefore responsible for sensing mechanical, thermal and chemical stimuli applied to the head/face. When compared to the ascending pain pathway described above, this specific pathway takes a different path to the thalamus. To begin, noxious stimuli are perceived by trigeminal ganglia neurons. These neurons have projections in the brainstem, to the spinal trigeminal nucleus (Sp5) in the medulla. From there, a second-order neuron relays the information to the thalamus.

Distribution and trafficking of DOPr in the CNS

As opioid peptides and their specific receptors play a critical role in the relief of pain, it is not surprising that MOPr, DOPr and KOPr are expressed in the CNS, along the pain pathways. For the purpose of this review, the distribution of DOPr will be further discussed. However, one may refer to a recently published interactive MOPr and DOPr brain atlas (Erbs et al. 2015). DOPr is highly expressed in the forebrain in regions such as the amygdala, the cortex, the striatum and the olfactory bulb (Mansour et al. 1994). Furthermore, some structures implicated in pain transmission such as the rostro-ventral medulla (RVM), the parabrachial nucleus, the hypothalamus, the thalamus and the periaqueductal gray area (PAG) contain DOPr (Erbs et al. 2015; Mansour et al. 1994). Interspecies differences in the distribution of DOPr were however observed. Indeed, autoradiography studies revealed that in mice and rats, DOPr is expressed throughout the spinal cord gray matter. Interestingly, in monkeys and humans, DOPr is mainly located in the superficial lamina (laminae I-II) (Mennicken et al. 2003).

If the presence of DOPr in various regions of the brain and in the ascending and descending pain pathways has been well documented (Cahill et al. 2001a; Mansour et al. 1995, 1994; Mennicken et al. 2003), the identity of DRG neurons expressing this receptor remains controversial. At first, DOPr was found in all types of DRG neurons (Dado et al. 1993; Gendron et al. 2006; Mansour et al. 1994; Mennicken et al. 2003). Using a genetically engineered mouse model, Scherrer and colleagues rather observed that a fluorescent DOPr chimera (DOPr-eGFP) was mainly expressed in large myelinated, non-nociceptive neurons (Bardoni et al. 2014; Scherrer et al. 2006). This is in sharp contrast with what was observed by others. Indeed, DOPr was found in large dense core vesicles (LDCV), associated with preprotachykinin A (Guan et al. 2005), as well as in substance P-containing terminals (Riedl et al. 2009). DOPr was also found to regulate substance P release from primary afferents (Beaudry et al. 2011; Kouchek et al. 2013; Normandin et al. 2013) and to synergize with the α2A-adrenergic receptors in peptidergic neurons (Schuster et al. 2013). Using the DOPr-eGFP mouse model, a very low level of coexpression between DOPr with substance P, CGRP or TRPV1 was observed (Scherrer et al. 2009). Absence of DOPr in small DRG neurons is also supported by single-cell RNA-sequencing of mouse sensory neurons (Usoskin et al. 2015). Nowadays, it remains unclear if this discrepancy comes from interspecies differences, lack of specificity in the approaches, or an artifact from the eGFP-tagged receptor.

Although DOPr is highly expressed in the CNS, its subcellular localization is atypical when compared to other class A G protein-coupled receptors (GPCRs). Indeed, various experimental approaches revealed that DOPr is mainly located in the cytoplasm, associated with various membrane structures and organelles, with a very low level of receptors being associated with the plasma membrane (Cahill et al. 2001a; Cheng et al. 1995; Gendron et al. 2006; Pasquini et al. 1992; Zhang et al. 1998). This particular location makes it harder to target DOPr and might explain why

selective DOPr agonists show only weak antinociceptive effects under normal conditions (Cahill et al. 2007; Zhang et al. 2010). We and others have however shown that the level of DOPr at the cell surface can be increased with a chronic treatment with morphine or under chronic pain conditions (Cahill et al. 2001a, b, 2003; Gendron et al. 2006; Lucido et al. 2005; Morinville et al. 2003, 2004). Most interestingly, this increase in DOPr at the cell surface is paralleled by an improvement of the analgesic effects of DOPr agonists (Cahill et al. 2001b, 2003; Gendron et al. 2007a, b; Morinville et al. 2003) as well as by an increase in DOPr functions (Hack et al. 2005; Pradhan et al. 2013a). Finding ways to improve the delivery of DOPr at the cell surface could therefore help identify novel analgesic compounds with reduced unwanted effects. Admittedly, increasing DOPr at the cell surface, including in chronic pain models, may as well reveal unwanted effects and reinforcement. In the context of chronic pain, measuring reinforcement of drugs is however challenging. Indeed, because pain is aversive, non-addictive drugs effectively produce place preference in chronic pain models (King et al. 2009).

Because they do not reach the brain, peripherally restricted agonists are devoid of centrally mediated unwanted effects affecting mood and emotions. As for central DOPr, peripheral DOPr appears to be incompetent and, to be effective, peripherally restricted DOPr agonists need some sort of priming (Gaveriaux-Ruff et al. 2008; Patwardhan et al. 2005, 2006; Pettinger et al. 2013; Rowan et al. 2009; Stein et al. 1989). In fact, although DOPr is present at the plasma membrane of peripheral sensory neurons, it is weakly activated following agonist binding (Brackley et al. 2016, 2017). Bradykinin (BK) is known to play an important role in the awakening of DOPr functionality in peripheral sensory neurons. In these neurons, GRK2 was found to constitutively associate with DOPr at the plasma membrane through a mechanism involving PKA and AKAP (Brackley et al. 2017). The GRK2–DOPr interaction prevents the association between DOPr and the Gβ subunit, and by way of consequence the agonist efficacy. Interestingly, BK was found to promote the dissociation of GRK2 and DOPr and to increase its association with Raf kinase inhibitory protein (RKIP). The protein kinase C (PKC)-dependent phosphorylation of RKIP sequesters GRK2, restoring the functionality of DOPr in peripheral sensory neurons (Brackley et al. 2016).

DOPr in pain conditions

DOPr agonists represent a great alternative to commonly used opioids to treat acute and chronic pain, because they produce fewer and milder unwanted effects. DOPr agonists also have anxiolytic and anti-depressive effects (Broom et al. 2002b, c; Chu Sin Chung and Kieffer 2013), two important comorbidities of chronic pain (Goldenberg 2010a, b). As stated above (but see also the next section), DOPr agonists have no or very weak antinociceptive effects in acute pain models. In addition, DOPr was not found to participate in the endogenous analgesic tone in normal animals submitted to acute pain tests (Filliol et al. 2000; Zhu et al. 1999). Interestingly, DOPr-KO mice are more sensitive to noxious stimuli in models of chronic inflammatory and neuropathic pain (Gaveriaux-Ruff et al. 2008; Nadal et al. 2006). Together, these observations suggest that DOPr plays an important role in modulating chronic pain, but is less effective against acute pain. The exact reasons why DOPr is more competent in chronic pain models than in acute pain models remain unclear. As mentioned above, the intracellular localization of the receptor in a naive state is one of the current working hypotheses. It is thought that under chronic pain conditions, DOPr expressed in neurons of the CNS can escape the maturation process more efficiently, increasing the density of membrane receptors (Gendron et al. 2016). Chronic pain may modify the interaction of DOPr with various proteins (kinases, chaperones, etc.) to promote this process (Beaudry et al. 2015b; Shiwarski et al. 2019; St-Louis et al. 2017; Xie et al. 2009). In the periphery, DOPr appears to stand incompetent at the plasma membrane of sensory neurons. Inflammation (this is to say chronic inflammatory pain) acts as a "priming" signal to reinstate the functions of DOPr and agonists efficacy. The mechanisms involved in this process have recently been reviewed elsewhere (Jeske 2019).

DOPr in acute pain models

Evidence for DOPr-mediated antinociceptive effects in acute pain tests are shown in Table 1.

Thermal pain

Thermal pain is usually used to test the acute reaction to a warm/hot stimulus such as hot water, radiant heat or a hot plate. Comparison of the latency to tail withdrawal is made before and after the administration of an analgesic compound. Generally speaking, MOPr agonists are known to produce more profound analgesia than DOPr agonists in such experimental settings. As an example, pioneer studies showed that the administration of the MOPr agonist DAMGO (H-Tyr-d-Ala-Gly-MePhe-Gly-ol) produces a more potent analgesia than the DOPr agonist [D-Pen2,5]-Enkephalin (DPDPE) in the hot plate test (Porreca et al. 1984). In the tail flick test, central or systemic administration of SNC80 (a delta-selective agonist) produced a time- and dose-dependent antinociceptive effect (Bilsky et al. 1995). The antinociceptive effect peaked at 10 min following the i.c.v. and i.t. administration and 30 min after the

Table 1 DOPr-mediated effects in acute pain models

Type	Test	Agonist	Route of administration	Animal species	References
Thermal pain	Tail flick	Deltorphin II	i.t	Mouse	Dubois and Gendron (2010)
	Tail flick (warm water)	SNC80	i.c.v i.t i.p	Mouse	Bilsky et al. (1995)
	Tail flick (light beam)	SB-235863	p.o. (No effect)	Rat	Petrillo et al. (2003)
	Hotplate	SNC80	i.c.v	Mouse	Bilsky et al. (1995)
	Hot plate	SB-235863	p.o. (No effect)	Rat	Petrillo et al. (2003)
	Tail flick (light beam)	Deltorphin II	i.c.v	Rat	Fraser et al. (2000a)
	Tail flick (light beam)	SNC80	i.c.v	Rat	Fraser et al. (2000a)
	Tail flick	DPDPE	Intra-RVM Intra-PAG (No effect)	Rat	Rossi et al. (1994)
	Tail flick	Deltorphin II	Intra-RVM Intra-PAG	Rat	Rossi et al. (1994)
	Hot plate	Deltorphin II	i.t	Rat	Cahill et al. (2001b)
	Hargreaves test	SNC80	i.t. (No effect)	Rat	Kouchek et al. (2013)
	Hargreaves test	Deltorphin II	i.t. (No effect)	Rat	Kabli and Cahill (2007)
	Tail flick	SNC80	s.c. (No effect)	Rat	Gallantine and Meert (2005)
Mechanical pain	von Frey test	SNC80	i.p. (No effect)	Mouse	Pradhan et al. (2013a)
	Paw pressure	Deltorphin II	i.c.v	Rat	Fraser et al. (2000b)
		SNC80	i.c.v	Rat	Fraser et al. (2000b)
Chemical pain	Capsaicin	Deltorphin II	i.t	Rat	Beaudry et al. (2011)
	Capsaicin (tail thermal hypersensitivity)	SNC80	s.c	Monkey	Brandt et al. (2001)
	Capsaicin (mechanical)	DPDPE	i.m	Rat	Saloman et al. (2011)
	Prostaglandin E2	SNC80		Monkey	Brandt et al. (2001)
	Formalin	Deltorphin II	i.t	Rat	Beaudry et al. (2011)
	Formalin	Deltorphin II	ipl	Rat	Kabli and Cahill (2007)
	Formalin	Deltorphin II	i.t	Mouse	Morinville et al. (2003)
	Formalin	Deltorphin II	i.t	Rat	Cahill et al. (2001b)
	Formalin	Deltorphin II	i.t ipl	Rat	Bilsky et al. (1996b)
	Formalin	Deltorphin II	i.t	Rat	Pradhan et al. (2006)
	Formalin	SNC80	ipl	Rat	Obara et al. (2009)
	Formalin	DSLET	ipl	Rat	Obara et al. (2009)
	Formalin	KNT-127	s.c	Mice	Saitoh et al. (2011)
	Formalin	SNC80	i.v	Mice	Barn et al. (2001)
	Formalin	SNC80	i.t	Rat	Kouchek et al. (2013)
	Acetic acid	KNT-127	s.c	Mice	Saitoh et al. (2011)
	Acetic acid	SNC80	s.c	Rat	Gallantine and Meert (2005)

i.p. injection of SNC80. SNC80 also produces antinociception in the hot plate test following i.c.v. administration, an effect that was blocked by the selective DOPr antagonist naltrindole (Bilsky et al. 1995). The antinociceptive effects of the peptidic DOPr-selective agonist deltorphin II was also described in various pain assays, including tail flick, hot plate and Hargreaves plantar tests (Cahill et al. 2001b; Dubois and Gendron 2010; Fraser et al. 2000a; Rossi et al. 1994).

Mechanical pain

Mechanical pain is often described as a sensitivity to mechanical stimuli. To test the acute mechanical pain, tests such as von Frey and paw pressure (Randall-Selitto test) can be used. A pioneer study showed that the i.c.v administration of either deltorphin II or SNC80 in rats produced a peak antinociceptive effect in the paw pressure test 15 min after the injection (Fraser et al. 2000b). Interestingly, the effects were similar in amplitude as the antinociception produced by i.c.v. DAMGO; this is to say that all three agonists were able to reduce the nociception by 80%, suggesting that both DOPr or MOPr produce equivalent analgesia in this model. By contrast, the effect of i.p. SNC80 in naïve mice and in CFA-treated mice assessed with the von Frey test revealed no effect of SNC80 in the naïve mice, but a significant antinociceptive effect was noted in CFA-injected mice (Pradhan et al. 2013a).

Chemical pain (acute inflammatory pain)

Even if, as described above, DOPr agonists produce weak antinociceptive effects in acute pain models, they were found to potently relieve acute inflammatory pain. Indeed, numerous groups confirmed the analgesic effects of delta agonists in both the capsaicin and the formalin tests. Deltorphin II was found to significantly reduce nocifensive behaviors induced by capsaicin and formalin in rodents (Beaudry et al. 2011; Bilsky et al. 1996a; Cahill et al. 2001b; Kabli and Cahill 2007; Morinville et al. 2003; Pradhan et al. 2006). The analgesic effects of SNC80 was also tested for chemical pain using different routes of administration (s.c., i.pl., i.v. and i.t.) and in various species. This agonist reduces pain-like behaviors induced by capsaicin and formalin (Barn et al. 2001; Brandt et al. 2001; Kouchek et al. 2013; Obara et al. 2009). Two groups have shown that the activation of DOPr produced an inhibition of substance P release as well as a decrease in c-fos expression within the spinal cord, suggesting that DOPr agonists are able to block noxious stimuli-induced spinal neurons activation (Beaudry et al. 2011; Kouchek et al. 2013).

DOPr in chronic pain models

DOPr agonists are known to produce robust antinociceptive effects in chronic pain models, possibly because the density of the receptor at the cell surface is increased under such conditions (Gendron et al. 2016). Indeed, DOPr agonists effectively alleviate pain in animal models of inflammatory, cancer, neuropathic and migraine pain. The effects of DOPr agonists in chronic pain models are summarized in Table 2.

Chronic inflammatory pain models: complete Freund's adjuvant (CFA) and carrageenan

Complete Freund's adjuvant (CFA) and carrageenan are often used as chronic inflammatory pain models. Although they do not perfectly mimic the human disease, they are often used as animal models of arthritis. In rat and mouse CFA models of inflammation, the i.t. injection of deltorphin II produced a time- and dose-dependent antihyperalgesic effects in the Hargreaves plantar test (Beaudry et al. 2009; Dubois and Gendron 2010; Gendron et al. 2007a). Deltorphin II also produced a dose-dependent, DOPr-mediated analgesic effect in the rat CFA model assessed for mechanical hypersensitivity with the von Frey test (Otis et al. 2011). Others have shown the efficacy of deltorphin II in this model using different routes of administration (Fraser et al. 2000a; Qiu et al. 2000). Another DOPr agonist derived from codeine was tested in the rat CFA model of inflammation using the plantar test. Subcutaneous injection of SB-235863 had a significant antihyperalgesic effect when compared to the vehicle group (Beaudry et al. 2009). SNC80 was also used in the plantar and the von Frey tests in the mouse CFA model. Both i.p. and s.c. injections of SNC80 produced antihyperalgesic and antiallodynic effects that were absent in DOPr-KO mice, supporting a specific role for DOPr (Gaveriaux-Ruff et al. 2008; Pradhan et al. 2013b). Similarly, i.c.v. and s.c. SNC80 induced antihyperalgesic effects in the rat CFA model of inflammation (Fraser et al. 2000a; Gallantine and Meert 2005). Interestingly, this small molecule agonist further produced analgesia in monkeys when administrated s.c. (Brandt et al. 2001). Finally, DPDPE injected i.t. or i.pl. produced analgesia in these models as well (Hervera et al. 2009; Qiu et al. 2000; Zhu et al. 1998).

Using carrageenan as the inflammatory agent, the four agonists mentioned above (Delt II, SB-235863, SNC80 and DPDPE) were also effective in reducing the thermal hyperalgesia and allodynia in rats following i.t. and p.o. administration (Kouchek et al. 2013; Petrillo et al. 2003; Stewart and Hammond 1994).

Cancer pain

Bone cancer-induced pain shares commonalities with both inflammatory and mechanical pain states. However, we know that it has its own characteristics and should therefore be considered in a different category (Honore et al. 2000). The putative analgesic effects of DOPr agonists were assessed in this paradigm by several groups. Following s.c. peritumoral injections of DPDPE 4 weeks after the inoculation of cancer cells (NCTC 2472) in mice, a dose-dependent analgesia was observed in the unilateral hot plate test (Baamonde et al. 2005). Using a different mouse model of bone cancer-induced pain, Brainin-Mattos and colleagues

Table 2 DOPr-mediated effects in chronic pain models

Type	Test	Agonist	Route of administration	Animal species	References
Inflammatory *CFA*	Thermal pain				
	Hargreaves plantar test	Deltorphin II	i.t	Rat	Beaudry et al. (2015a, 2009;) Cahill et al. (2003;) Gendron et al. (2007a)
		Deltorphin II	i.t	Mouse	Beaudry et al. (2009;) Cahill et al. (2003;) Dubois and Gendron (2010;) Gendron et al. (2007b)
		Deltorphin II	i.c.v	Rat	Fraser et al. (2000a)
	Hargreaves plantar test	SNC80	i.c.v	Rat	Fraser et al. (2000a)
	Hargreaves plantar test	SB-235863	s.c	Rat	Beaudry et al. (2009)
	Hargreaves plantar test	DPDPE	ipl	Mouse	Hervera et al. (2009)
	Tail flick	SNC80	s.c	Monkey	Brandt et al. (2001)
	Hargreaves plantar test	SNC80	s.c	Rat	Gallantine and Meert (2005)
	Hargreaves plantar test	SNC80	s.c	Mouse	Gaveriaux-Ruff et al. (2008)
	Mechanical Pain				
	von Frey filament	Deltorphin II	i.t	Rat	Otis et al. (2011)
	von Frey filament	SNC80	i.p	Mouse	Pradhan et al. (2013a)
	Paw pressure test (Randall-Stelitto)	DPDPE	ipl	Rat	Zhou et al. (1998)
	von Frey filament	SNC80	s.c	mouse	Gaveriaux-Ruff et al. (2008)
Carrageenan	Thermal pain				
	Hargreaves plantar test	SB-235863	p.o	Rat	Petrillo et al. (2003)
	Mechanical pain				
	von Frey filament	SNC80	i.t	Rat	Kouchek et al. 2013
Cancer pain	Mechanical pain				
	von Frey filament	Deltorphin II	i.t	Rat	Otis et al. (2011)
	von Frey filament	[dVal(L)2,Ala(L)5]E	i.p	Mouse	Brainin-Mattos et al. (2006)
	von Frey filament	SNC80		Mouse	Ye et al. (2012)
	Thermal Pain				
	Unilateral Hotplate test	DPDPE	Peritumoral	Mouse	Baamonde et al. (2005)
Diabetic neuropathy	Tail flick	TAN-67	i.c.v	Mouse	Kamei et al. (1997b)
	Formalin	TAN67	s.c	Mouse	Kamei et al. (1997a)
Neuropathic pain	Thermal Pain				
	Hargreaves plantar test	DSLET	ipl	Rat	Obara et al. (2009)
		SNC80	ipl	Rat	Obara et al. (2009)
	Hargreaves plantar test	SB-235863	p.o	Rat	Petrillo et al. (2003)
	Noxious thermal stimuli (paw)	Deltorphin II	i.t	Rat	Holdridge and Cahill (2007)
	Tail flick (Cold allodynia)	Deltorphin II	i.t	Rat	Mika et al. (2001)
	Tail flick (heat and cold stimuli)	Deltorphin II	i.t	Rat	Mika et al. (2001)
	Tail flick (cold allodynia)	DPDPE	i.t	Rat	Mika et al. (2001)
	Tail flick (heat and cold stimuli)	DPDPE	i.t	Rat	Mika et al. (2001)
	Acetone application	DPDPE	Intra-PAG	Rat	Sohn et al. 2000
	Mechanical pain				
	von Frey filament	Deltorphin II	ipl	Rat	Kabli and Cahill (2007)
	von Frey filament	Deltorphin II	i.t	Rat	Holdridge and Cahill (2007)
	von Frey filament	SNC80	ipl	Rat	Obara et al. (2009)
	von Frey filament	DSLET	ipl	Rat	Obara et al. (2009)
	von Frey filament	DPDPE	Intra-PAG	Rat	Sohn et al. (2000)
	Paw pressure	BUBU	i.v	Rat	Desmeules et al. (1993)

Ipl. Intraplantar, *s.c.* subcutaneous, *i.t.* intrathecal, *i.m.* intramuscular, *i.c.v.* intracerebroventricular, *i.p.* intraperitoneal, *p.o.* perorally, *i.v.*intravenous

found that an intraperitoneal injection of [dVal(L)2,Ala(L)5]E was effective in reducing allodynia (Brainin-Mattos et al. 2006). Interestingly, the maximal effect produced by this DOPr agonist was comparable to the effects observed following morphine injection (Brainin-Mattos et al. 2006). Calculation of the ED_{50} for morphine (5.29 ± 1.91 mg/kg) and [dVal(L)2,Ala(L)5]E (1.34 ± 0.31 mg/kg) confirmed the high potency of the DOPr agonist in this model (Brainin-Mattos et al. 2006). In other studies, i.pl. SNC80 and i.t. deltorphin II were also able to reduce the mechanical pain induced by von Frey hairs in mouse and rat models of cancer pain (Otis et al. 2011; Ye et al. 2012).

Neuropathic pain

Preclinical models of neuropathic pain were used to test the effects of DOPr agonists in this specific condition. Using a model of sciatic nerve injury in Wistar rats, deltorphin II and DPDPE injected intrathecally produced an antiallodynic effect in thermal pain tests (Mika et al. 2001). The effects of deltorphin II was also assessed in a model of chronic constriction injury with the thermal pain test (cold) and the von Frey test (Holdridge and Cahill 2007). Deltorphin II was found to produce anti-hyperalgesia and an anti-allodynic effects 14 days after the injury (Holdridge and Cahill 2007). Other DOPr agonists such as DSLET, SNC80 and SB-235863 proved to be potent in preclinical models of neuropathic pain in rats (Obara et al. 2009; Petrillo et al. 2003).

Migraine pain

Drugs such as triptans (sumatriptan) are often used for the treatment of migraine, but in some case patients remain unresponsive. In some instance, such as the severity of migraine, MOPr agonists can be used (Bigal and Lipton 2009; Buse et al. 2012; Thorlund et al. 2016). However, a phenomenon called opioid-induced hyperalgesia (OIH) can appear in patients using opioids repeatedly for migraine headaches. In fact, the use of morphine is only rarely devoid of undesired effects. When used to treat migraine, opioids were found to play a key role in the transition from episodic to chronic migraine problems (Bigal and Lipton 2009; Buse et al. 2012; Thorlund et al. 2016). If the use of MOPr agonists is worrisome at a time when we face a major opioid crisis, the difference in DOPr and MOPr expression in the trigeminal complex could lean toward DOPr as a great alternative. Using [^{125}I]-deltorphin II, Mennicken and colleagues revealed the distribution of DOPr in the Sp5 of rats and humans (Mennicken et al. 2003). They also described the distribution of DOPr mRNA in the Sp5 of rats and humans. A recent review by Charles and Pradhan summarized these observations and discussed the potential of DOPr agonists for the treatment of migraine (Charles and Pradhan 2016).

In recent years, several groups have developed preclinical models of rodents to test new migraine therapies. Among these models, nitroglycerin (NTG) and isosorbide dinitrate (ISDN), two nitric oxide donors, were used to mimic migraine headaches (Dallel et al. 2018; Pradhan et al. 2014). Using the NTG model, Pradhan and colleagues showed the effectiveness of SNC80 to produce an antiallodynic effect similar to the one seen with sumatriptan (the most used treatment for migraine) (Moye et al. 2019a, b). SNC80 was able to reduce the thermal and mechanical hyperalgesia induced by NTG (Pradhan et al. 2014). In addition, at 10 mg/kg, the DOPr agonist injected i.p. reversed the conditioned place aversion caused by the NTG administration (Pradhan et al. 2014). Cortical spreading depression (CSD), which is a migraine symptom often correlated with migraine accompanied by aura, was also inhibited by SNC80 as measured by electrophysiological procedures (Pradhan et al. 2014). Using the ISDN model, a cephalic and extracephalic mechanical hypersensitivity was observed and correlated with a migraine progression depending on the number of doses of ISDN given to rodents (Dallel et al. 2018). Treatments usually prescribed for migraine therapy such as olcegepant, sumatriptan and propranolol were also tested in this second migraine model. All three treatments showed analgesic efficacy, but only under specific conditions. For example, olcegepant significantly reduces the cephalic allodynia after a single and after repeated injections of ISDN (10 mg/kg, i.p.), but sumatriptan only alleviates the cephalic allodynia after a single injection of ISDN (Dallel et al. 2018). Propranolol, known as the preventive therapy for migraine treatment, significantly reduced the cephalic allodynia only after repeated doses of ISDN (Dallel et al. 2018). These interesting results provide a new migraine model similar to the NTG one and may be another model on which the analgesic potential of delta agonists could be investigated. In parallel, studying these two models will also provide a better understanding of the migraine mechanisms.

Development of analgesic tolerance to DOPr agonists

Because a large body of evidence showed a great efficacy of DOPr agonists in different pain models (see above), their potential as alternative therapeutics is of considerable interest. However, a possible problem that arises from the use of such molecules is the fact that tolerance can rapidly develop making them less adapted to the treatment of chronic pain. Indeed, it was found that the high-internalizing agonist SNC80 results in the desensitization of DOPr and produces analgesic tolerance (Pradhan et al. 2016). Arrestin 2 was found to play an essential role in this process, since in KO mice drug potency and duration of action are increased,

while acute tolerance to the antihyperalgesic effects of SNC80 is reduced (Vicente-Sanchez et al. 2018). However, low-internalizing agonists ARM390 and JNJ20788560 do not produce tolerance unless arrestin 3 is depleted (Pradhan et al. 2016). Absence of tolerance in animal models of pain was also observed with another low-internalizing agonist, SB-235863 (Beaudry et al. 2009; Petrillo et al. 2003). More recently, it was observed that agonists supporting recycling of DOPr produce minimal tolerance (Audet et al. 2012; Charfi et al. 2018). The fact that the development of analgesic tolerance is agonist dependent raises the possibility of developing a drug with minimal risk of tolerance.

DOPr in clinical trials

As described above, DOPr agonists represent a tempting target for the treatment of chronic, inflammatory, neuropathic and migraine pain. As DOPr produces less respiratory depression, tolerance and constipation than MOPr agonists, its activation represents a promising alternative to commonly used opioids. One of the major problems with DOPr agonists is their propensity to induce nonlethal convulsions (Broom et al. 2002a, d; Chung et al. 2015). This adverse effect makes it difficult to bring such molecules to the clinic. Nonetheless, DOPr agonists have reached clinical trials for the treatment of various pathologies and conditions, including pain (Spahn and Stein 2017). Two compounds, ADL5747 and ADL5859, were tested in clinical trials for pain problems (Le Bourdonnec et al. 2008, 2009). In phase I clinical trial, ADL5859 did not induce the adverse events often seen with DOPr agonists (convulsions and locomotor alterations) even with doses as high as 1000 mg/kg. Unfortunatley, ADL5859 showed no better effect than the placebo and ibuprofen after dental surgery. Following this result, three other studies used the DOPr agonist for inflammatory rheumatoid arthritis, diabetes-induced peripheral neuropathy and osteoarthritic pain. No significant findings emerged from these trials. Again, a lack of efficacy over placebo was reported. Two phase II clinical trials looking at the therapeutic effects of ADL5747 in osteoarthritic pain and postherpetic neuralgia were also performed. As for ADL5859, in these trials the parent compound ADL5747 was not more effective than the placebo. The exact reasons why these compounds failed to produce significant analgesic effects in these trials remain unknown. One can argue that the design of the trial was not optimal. Indeed, it is worth mentioning that oxycodone, used as a positive control, also failed to produce a better analgesic effect than the placebo. New trials are certainly needed before we can conclude on the potential therapeutic effects of DOPr agonists.

Conclusion

As described in this review, targeting DOPr represents a promising alternative to develop novel therapies for the treatment of chronic inflammatory, neuropathic, cancer and migraine pain. Despite the current evidence for the analgesic effects of DOPr agonists under each condition, more research is needed to better understand the mechanisms involved in DOPr trafficking, but also to better describe its role in modulating pain.

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