

# Cardioprotective actions of opioids in the ischemic heart: bypassing occlusions in our current knowledge

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## Abstract

Opioids are extensively utilized therapeutically for management of chest pain during various heart conditions such as, myocardial infarction (MI) and ischemic heart disease (IHD). Emerging literature about the chronic cardiovascular effects of opioid use remains elusive and controversial. While several studies have reinforced the cardioprotective effects of opioid receptor activation in various rodent and animal models, these effects are less established in humans. Other studies have examined the clinical outcomes of opioid use and there is still much division in our understanding. While some of these studies suggest there are no cardiovascular effects, others indicate there are adverse effects including a greater risk for stroke, coronary heart disease and even death. This review paper aims to examine current understandings on the cardiovascular effects of opioids based on experimental and clinical evidence.

## Introduction

Both ischemic heart disease (IHD) and myocardial infarction (MI) remain the leading causes of cardiovascular mortality and morbidity in North America, with IHD accounting for 60% of all cardiovascular deaths in Canada.<sup>1</sup> While endogenous opioids are known to play several key roles in the control of the nervous system, suppression of pain, and regulation of bowel movements, there has also been a growing body of experimental evidence showing that these opioid peptides and their receptors are critically implicated in the protection of the heart against ischemia.<sup>2-5</sup> In light of these findings, studies have become optimistic about translating this understanding of the mechanisms and actions of opioids and their receptors to clinical settings in the therapeutic management of IHD and MI. However, in spite of strong experimental evidence from animal and human tissue models, little is still understood about efficacy and chronic effects of exogenous opioids in clinical populations.<sup>6</sup> Additionally, there are adverse risks characteristic of opioid use for recreational purposes

such as sedation, dizziness, nausea, vomiting, constipation, physical dependence, psychological addictions, tolerance, and respiratory depression, among many. Furthermore, within the context of the current opioid crisis, opioid abuse has created a deterring climate for research on mechanisms of opioid-induced cardioprotection. In light of this, this paper does not recommend increased or chronic prescription of opioids for their cardioprotective effects, but rather reviews the mechanisms of cardioprotection. The objectives of this review are to explore the existing (i) experimental and (ii) clinical understanding of cardioprotective effects of opioids in the heart and their actions after receptor activation.

This review sought to examine both basic science and clinical literature, and as such was designed to identify studies reporting the use of opioids in management of any form of cardiac ischemia and its outcomes, in addition to exploring the mechanisms of action of opioids. Databases including PubMed/MEDLINE, EMBASE, and Google Scholar were utilized and no time, setting, or language restrictions were imposed on the search strategy. Primary research articles, including case studies, and non-primary studies, including systematic reviews and meta-analyses, were additionally included. Any study concerning the use of opioids for management of non-cardiac pain or anesthesia was excluded from this review.

## Endogenous Cardiac Opioid Peptides

All known classes of endogenous opioids in the heart can be divided into three major classes: endorphins, enkephalins, and dynorphins, with each of these classes associated with their own family of opioid receptors (Table 1). Although opioids were traditionally understood to be a family of pain-relief peptides derived only from neural sites, it is now well established that these peptides are also widely expressed and distributed in non-neural tissues, including cardiomyocyte tissues of multiple species such as rodents, cats, rabbits, guinea pigs, and humans.<sup>7,9</sup> In rodents, endogenous opioids such as met-enkephalin and dynorphin A and B significantly increase in expression levels under conditions of myocardial ischemia.<sup>10,11</sup> This suggests that opioids that are synthesized by cardiac tissue are involved in a mechanism to attenuate ischemia in the heart. As there are opioid receptors in the heart, the localization of opioid peptide synthesis in the heart could potentially indicate that control of cardiac function relies on an autocrine or paracrine mechanism.

The anti-ischemic actions of opioids have been compared to ischemic preconditioning, defined as an experimental strategy involving repeated short episodes of ischemia prior to a later ischemic insult with a purpose of mitigating tissue damage from loss of blood supply and oxygen during the insult.<sup>12</sup> Moreover, the nonselective blockade of opioid receptors within the heart inhibits the protective effects conferred by ischemic preconditioning

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suggesting that endogenous opioids are integral for this mechanism to occur.<sup>13</sup> Apart from anti-ischemic effects, endogenous opioids have also been suggested to play other key roles in cardioprotection such as increasing survival in mice and rabbits following hypoxia and reducing infarct size in MI-induced rats.<sup>14,15</sup> Understanding the structure and function of these endogenous opioids is critical in the context of designing novel therapeutics to mimic their actions. To better elucidate the actions of these opioids, it is equally important to examine the mechanisms and functions of opioid receptors.

**Table 1.** Action and Selectivity of Endogenous and Exogenous Opioids at Various Opioid Receptors

Opioid	Receptor type		
	Mu - $\mu$	Delta - $\delta$	Kappa - $\kappa$
Endogenous opioids			
Met-enkephalin	++	+++	
Leu-enkephalin	++	+++	
Beta-endorphin	+++	++	
Dynorphin-A	+	+	+++
Exogenous opioids			
Morphine	+++	+	+
Fentanyl	+++		+
Remifentanyl	+++		
Sufentanyl	+++	+	+
Methadone	+++	+++	+
Codeine	+		

+++ , potent effect; ++ , moderate effect; + , weak effect; blank, no significant effect

### Opioid Receptors in the Heart

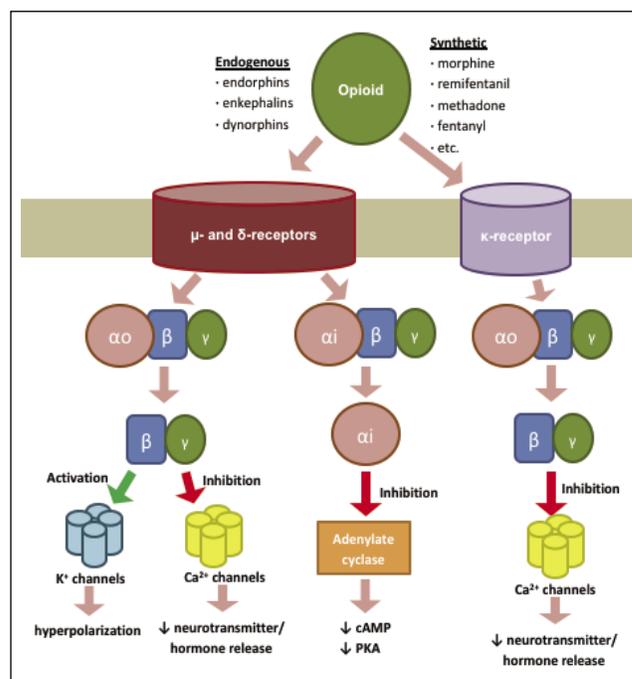
The classical mechanism of action for opioids involves the binding of the opioid to a class of inhibitory G protein-coupled receptors.<sup>2,16</sup> These receptors can be further subdivided into 3 main classes of receptors: mu ( $\mu$ ), delta ( $\delta$ ), and kappa ( $\kappa$ ). In neurons, these receptors generally act by either inhibiting the adenylyl cyclase pathway or acting directly to activate  $K^+$  or inhibit  $Ca^{2+}$  channels to generate hyperpolarization in the postsynaptic cell, thereby suppressing hormonal or neural transmission (Figure 1). The same classes of receptors have also been identified in the heart.<sup>17</sup>

#### $\mu$ -opioid Receptors

The literature surrounding the involvement and actions of  $\mu$ -opioid receptors in ischemia is still widely contested.<sup>17-19</sup> Initially,  $\mu$ -receptors were not thought to be involved in ischemia. One reason for this could have been the absence of  $\mu$ -opioid receptors in the rat heart [20]. Another factor may have been conflicting evidence. Of the endogenous opioid peptides, beta-endorphins, which have the greatest affinity for  $\mu$ -receptors (Table 1), had a minimal effect in conferring protection against ischemia in rabbits.<sup>21</sup> Additionally, it was shown in rats that an exogenous  $\mu$ -receptor selective opioid agonist, D-Ala,2N-Me-Phe,4glycerol5-enkephalin (DAMGO), did not have an effect in reducing tissue damage after ischemia.<sup>15</sup>

However, at the same time, administration of morphine, which was both a clinically important exogenous opioid agent and selective for the  $\mu$ -receptor, was observed to produce effects mimicking those

seen in ischemic preconditioning in rats.<sup>22</sup> Similar effects were seen with remifentanyl, another selective  $\mu$ -receptor agonist in isolated human heart tissue.<sup>23</sup> Later, it was shown that the cardioprotective effect of remifentanyl, when administered to an isolated perfused heart, was not blocked even following  $\mu$ -receptor blockade, which was in line with the earlier findings that  $\mu$ -receptors were not present in the rat heart.<sup>24</sup> As a result, it was concluded that remifentanyl acted via an indirect mechanism on the heart through extracardiac  $\mu$ -receptors. Although this does provide insight into a mechanism of action for opioids binding the  $\mu$ -receptor, it is challenging to make the same conclusion for morphine, as it may still exert effects on the  $\delta$ - and  $\kappa$ -receptors. Finally, it is difficult to extend these results to humans, as several species-dependent differences exist, such as the absence of myocardial  $\mu$ -receptors in rats. However, these findings might support the proposition that extracardiac opioid receptors are playing an indirect role in cardioprotection.



**Figure 1.**

#### $\delta$ -opioid Receptors

Of all opioid receptors, the  $\delta$ -opioid receptor is the best characterized within the heart. Its effects have been identified in rodent, murine, swine, and leporine models and it has been discovered to have critical implications in mimicking ischemic preconditioning from early work with its enkephalins and other exogenous opioid ligands.<sup>25-28</sup> Furthermore,  $\delta 1$ - and  $\delta 2$ -opioid receptor subtypes have been identified in these studies, with the former demonstrating more significant implications in cardioprotection.<sup>15-25</sup> The importance of these receptor subtypes in the heart was assessed by a reduction in size of MI after the selective blockade of  $\delta 1$ -receptors using 7-benzylidenenaltrexone (BNTX), which could not be replicated when  $\delta 2$ -receptors were blocked using the selective naltriben antagonist.<sup>15</sup> Additionally, the stimulation of these  $\delta$ -receptor subtypes in the heart was noted to be involved in proliferation

of ventricular myocytes and to mediate anti-apoptotic effects through the activation of a signaling pathway with extracellular signal-regulated kinase (ERK).<sup>29,30</sup> As ERK signaling is known to be a widespread intracellular signaling molecule in numerous cell systems, its activation perhaps indicates an overlap in the signaling mechanism utilized for ischemic cardioprotection.

Other studies have examined other aspects of the second messenger cascade and downstream signaling in the  $\delta$ -receptor cardioprotection pathway for ischemia such as the involvement of protein kinases including protein kinase C (PKC) and  $K^+$  channels. For example, one study utilized various antagonists of PKC subtypes including the PKC-delta antagonist, rottlerin, and found that PKC-delta but not the other subtypes of PKC was a necessary second messenger for  $\delta$ 1-receptor activation-induced myocardial ischemia protection in rats.<sup>31</sup> Another study by the same group utilized a similar method using a selective inhibitor for mitochondria ATP-sensitive  $K^+$  (KATP) channels including 5-hydroxydecanoic acid for mitochondrial KATP channels. They determined that blockade of these channels produced a cardioprotective effect that was significantly delayed resulting in metabolic inhibition, which causes cell death and a disruption of calcium homeostasis.<sup>32</sup> Later, these KATP channels were found to be activated by the presence of reactive oxygen and nitrogen species, which could increase under ischemic conditions and were proposed to play a role in ischemic preconditioning.<sup>33</sup> When integrated with the classical Gi signaling pathway involving the inhibition of cAMP, these kinases and channels can be understood as components of the downstream signaling cascade. Based on the close association of ERK signaling pathways with protein kinases and  $K^+$  channels, these findings point to a possibility that these kinases and channels may be a part of one system or share parts of the same signaling pathway. In addition to this, these findings also link redox signaling as an underlying mechanism for responding under ischemic conditions offering a conceivable explanation as to how the  $\delta$ -receptor signaling cascade modulates downstream effects.

In recent studies, similar to  $\mu$ -receptors,  $\delta$ -receptors implicated in regulation of cardiac functions have also been suggested to be located in extracardiac sites, namely sensory afferent nerves to the heart. Since  $\delta$ -receptors were known to be involved in the growth of neonatal ventricular myocytes, these sites were first investigated in the neonatal rat heart, which led to its identification in sensory afferent fibers that stained positive for Substance P and calcitonin gene-related peptide (CGRP).<sup>34</sup> Even more recently, in addition to myocardial cells,  $\delta$ -receptors have been identified in the CGRP-immunoreactive sensory neurons of human heart tissue.<sup>17</sup> Not only do these findings suggest an alternative mechanism for cardioprotection, they also open the door for greater considerations for more indirect mechanisms of opioid action involving the peripheral and central nervous system.

### $\kappa$ -opioid receptors

Of the other two opioid receptor classes, the  $\kappa$ -receptors are most similar to the  $\delta$ -receptors, although they are not as well characterized. In addition to the finding that dynorphins are implicated under ischemic conditions in the rabbit heart, the application of exogenous  $\kappa$ -receptor opioid agonists and antagonists in rodent and murine models has been shown to induce and block cardioprotection, respectively.<sup>35</sup> Upon activation,  $\kappa$ -receptors have

inhibiting effects on contraction and on the intracellular  $Ca^{2+}$  transient, which is electrically induced in cardiomyocytes.<sup>36</sup> Like  $\delta$ -receptors, both PKC and KATP channels are again involved in mediating ischemic protection. However, instead of PKC-delta, PKC-epsilon has been suggested to be responsible for delayed cardioprotection through mitochondrial KATP channels in its place. Furthermore, the metabolic inhibition and  $Ca^{2+}$  overload produced by ischemic conditions are counteracted by  $\kappa$ -receptors.<sup>37</sup> Once again, the signaling mechanisms by which  $Ca^{2+}$  homeostasis is restored may interact or share a common mechanism with the involvement of components from the classical model of  $\kappa$ -receptor signaling seen in the nervous system, particularly the  $Ca^{2+}$  channels (Figure 1).

Like  $\mu$ - and  $\delta$ -receptors,  $\kappa$ -receptors have been found in tissues outside of the heart suggesting the possibility of indirect effects in cardioprotection. Histologically,  $\kappa$ -receptor immunoreactivity is found predominantly in myocardial cells and long fusiform cells with an eccentrically located large nucleus that resembles intrinsic cardiac adrenergic (ICA) cell-like structures.<sup>17</sup> A possible mechanism that could be postulated by this finding is one whereby  $\kappa$ -receptor stimulation may result in enhanced cardioprotection via the modulation of epinephrine release from these ICA cell-like structures. Alternatively, the presence of  $\kappa$ -receptors on these structures could also be due to a suppressive function, such as inhibition of transmitter release, which can be achieved through the activation of the G0 signaling cascade. As  $\kappa$ -receptors are essential for  $Ca^{2+}$  release and cardiac contractility, its functions in cardioprotection could be more difficult to isolate.

### Cardiac Effects of Opioids in Humans

Although prevention has been directed at reducing risk factors for IHD and MI, other treatment strategies, such as administration of antiplatelet and antithrombotic agents, stenting, and ischemic preconditioning and postconditioning, have been implemented for management in clinical settings.<sup>38,39</sup> When compared to experimental animals, humans may have intrinsically different physiological responses to opioids, and studying the human heart is indispensable to ensure validity. Presently, both *in vitro*, and *in vivo* studies have been utilized to assess the effects of exogenous opioids on ischemia in humans.

### *In vitro* Studies

Of the experimental studies discussed, several *in vitro* studies have been performed on isolated heart tissue from human patients. For instance, human heart tissue obtained during autopsy after sudden death was utilized in one study to determine the localization of opioid receptor subtypes based on immunoreactivity levels in the heart.<sup>17</sup> In another *in vitro* study, plasma dialysate containing endogenous factors that activate opioid receptors were used to induce potent protection against myocardial ischemia and reperfusion injury in isolated cardiomyocytes.<sup>40</sup> Similar protective effects observed in ischemic preconditioning were also observed when the  $\delta$ -receptors on isolated atrial trabeculae tissue from patients who underwent coronary bypass grafting were activated by an exogenous  $\delta$ -receptor agonist.<sup>41</sup> Additionally, a mitochondrial KATP channel blocker was observed to abolish this effect.<sup>41</sup> Based on these results, it seems likely that opioid agonists work in an analogous fashion in humans to animal models such as rodents.

In addition to responding to similar exogenous opioids that act on the same receptor classes, many of these studies suggest a similar signaling mechanism for cardioprotection in humans too. However, *in vitro* evidence in humans is still limited and not as well characterized as in animal models.

### *In vivo* Studies

Presently, clinical evidence for opioid-induced cardioprotection in humans remains controversial and vague. Although there is minimal research, if any, that has examined  $\delta$ - or  $\kappa$ -receptor agonists in clinical populations affected by myocardial ischemia or infarction, a significant body of clinical research has attempted to evaluate the effects of  $\mu$ -receptor opioid agonists. In the secondary analysis of a recent clinical trial, the specific effects and safety of morphine in the treatment of patients with acute anterior ST-segment elevation MI were assessed, presenting no adverse effects for one year.<sup>42</sup> However, in a similar prospective cohort study conducted over a 4-year timespan, the use of prescription opioids, namely  $\mu$ -receptor agonists, was demonstrated to increase the risk of cardiovascular morbidity and coronary heart disease, both conditions that could increase ischemia chronically, in female patients.<sup>43</sup> Although the former study is consistent with experimental evidence, the latter revealed that it is more difficult to make solid conclusions due to variables such as the complexity and variation in humans along with the limitations of establishing controlled clinical studies. Another factor to consider is the method of administration compared to experimental studies. While administering an intravenous injection may allow the exogenous opioid to act on tissues, there may be limitations caused by absorption, distribution, and metabolism that may not have the same effect as direct application of opioids to the tissue, such as during an open heart surgery.

In fact, several clinical studies have focused on comparing opioid effectiveness in patients who undergo cardiac surgery procedures. For instance, in one clinical prospective randomized study, the effectiveness of morphine compared to fentanyl on the recovery of myocardial function following a coronary artery bypass graft (CABG) surgery was assessed, showing that global ventricular function was enhanced by morphine administration prior to ischemia resulting from cardioplegic arrest.<sup>44</sup> In another randomized controlled trial, myocardial injury from ischemia was effectively managed by late remote ischemic preconditioning but exacerbated by tramadol, an opioid  $\mu$ -receptor agonist, when it was administered orally before patients underwent CABG surgery.<sup>45</sup> In the former study, although the evidence is in line with experimental data that morphine has a greater effectiveness than fentanyl in inducing a cardioprotective effect, it is difficult to determine if this effect had to do with a different affinity for  $\mu$ -receptors or due to the supplementary action of morphine as a partial agonist in relation to fentanyl. For the latter, it appears that tramadol, despite being an opioid  $\mu$ -receptor agonist, had adverse effects on ischemia. One critical factor to consider in this case is the method of administration. While *per os* is the safest form of drug administration in patients, there could be resulting constraints on its effects. Indeed, the possibility that it was localized to another tissue, metabolized, or excreted without being absorbed in the bloodstream cannot be excluded since the study neither infused nor applied tramadol directly on the cardiac tissue.

### Future Avenues

In current clinical practice, although opioid analgesics such as morphine, fentanyl, meperidine, and methadone are extensively utilized for the management of pain, they have yet to be approved or recognized as a form of treatment for ischemia management and cardioprotection. This may be largely attributed to the scarce amount of research done in humans. Additionally, factors such as social concerns surrounding opioid abuse, dependence, and their effects on respiratory distress may limit not only their application in practice but also hinder the progress of research in humans. Coupled with this, the need to balance a design that ensures patient safety with the demands of producing conclusive clinical evidence for implementation can be challenging. The present review has elucidated a number of key areas where further exploration may offer greater advances to current understandings.

While the cardioprotective actions of  $\delta$ -receptor activation have gained the most momentum showing much promise in experimental investigations with reference to the other two opioid receptor classes, there is an utter lack of assessment for its effects in humans in clinical studies. Therefore, one avenue of research should be to explore its specific effects in a clinical population. Recently, the effectiveness of oral  $\delta$ -receptor agonists ADL5859 and ADL5747 have been examined in considering their effects on the management of pain, having passed phase I clinical trials.<sup>46</sup> If these exogenous opioid agonists are shown to pass the other phases for this trial, the next steps could be to examine their effects on different animal models and subsequently design a clinical trial where patients are provided oral doses of these drugs prior to CABG to examine their effects on enhancing ischemia/reperfusion injury in the heart. Another focus area to study may be the affinities of drug types to specific opioid receptors.

Some other missing links in our current knowledge are the signaling mechanisms and pathways by which opioid receptor classes are exerting downstream effects within the heart. The existing body of evidence in experimental models have only partially characterized these pathways as the involvement of signaling components comparable to neural systems and transduction signals such as subtypes of PKC and mitochondrial KATP channels in  $\delta$ - and  $\kappa$ -receptors. The involvement of redox signaling in the detection and mediation of ischemia also appears to be implicated in these processes and could be investigated in future research. Another idea suggested in multiple experimental studies was that extracardiac tissue opioid receptors may be involved in cardioprotection during ischemia. Future investigations can assess this idea by isolation or tissue-specific blockade in nerves, nuclei, or proposed extracardiac sites, as our current knowledge concerning these mechanisms still remain incomplete.

### Conclusions

Literature surrounding opioidergic cardioprotection under ischemic conditions remains in its embryonic stages and an emerging need exists for further exploration. However, current research garners much promise and growing evidence has contributed immensely to present understandings. Specifically, current research suggests that (i) affinity and response in different endogenous opioid peptides and synthetic commercial opioids have an independent association, (ii) there are both cardiac and extracardiac sites of opioid synthesis and storage where autocrine/

paracrine or endocrine signaling is possible under ischemia, (iii) several complex signaling pathways involving ubiquitous second messengers, such as PKC and K<sup>+</sup> channels in  $\delta$ - and  $\kappa$ -receptors, have been identified and proposed for opioidergic signaling, (iv) nearly all opioids show a degree of selectivity to  $\mu$ -receptors and selective targeting of the other receptor subtypes may be a promising direction, (v) clinical studies are inconclusive, and (vi) both in vitro and clinical studies in humans are still warranted. This review does not suggest that opioids should be prescribed increasingly or chronically for their cardioprotective effects, but instead highlights the emergent need for further research into ways these results can be used to increase survival in cardiac patients.

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