Opioids and neovascularization; pro or anti?

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Opioid receptors

Because of their potent and efficacious analgesic effects, opioids are the most commonly used medication for perioperative pain and pain as a result of cancer; however, their uses are extended to other conditions including cough1 and diarrhoea.2 Despite this, they are associated with a wide range of adverse effects such as tolerance, nausea and vomiting and respiratory depression.3 In addition, long-term use of opioids may cause hormonal disturbances secondary to hypothalamic-pituitary malfunction.4 Moreover, the presence of opioid receptors in non-CNS tissues results in various systemic impacts.5 In addition opioids can modulate immune function at non-leucocyte targets.6

Opioid receptors are members of the G protein coupled receptor (GPCR) superfamily.7 Classical naloxone sensitive opioid receptors are classified as MOP (µ; mu), DOP (δ; delta) and KOP (κ; kappa). In addition the non-classical receptor for Nociceptin/OrphaninFQ (N/OFQ), NOP, is a member of this family.8 NOP is naloxone insensitive. Once endogenous ligands or exogenous drugs stimulate opioid receptors, two activation pathways are engaged.9 The most well known pathway involves G-protein (guanine nucleotide binding protein) activation and subsequent inhibition of adenyl cyclase (reducing cyclic AMP), activation of an outward K+ current and closing of voltage gated Ca2+ channels.10 The second, pathway is responsible for receptor desensitization via internalization.11 Opioid receptors are phosphorylated by GPCR kinases, resulting in the recruitment of β-arrestin and the non-receptor tyrosine kinase C-Src. This complex is internalized in clathrin- lined pits before either recycling to the cell surface or degradation.10–12 Both pathways may end with stimulation of mitogen-activated protein kinases (MAPK); particularly extracellular-signal-regulated kinases (ERK) 1 and 2 pathway13 and both are linked.

VEGF signalling and angiogenesis

Angiogenesis is defined as a process of new blood vessel formation.13 Although this generic definition is adopted by many, it is hard to distinguish between angiogenesis, arteriogenesis, vasculogenesis and neovascularization.14 While neovascularization covers all other terms and may refer to any type of new vessel creation, angiogenesis is limited to the generation of new capillary plexuses from already established blood vessels. These capillaries are composed from endothelial cells only without any supporting vascular wall structure, apart from pericytes and basement membrane.14

Vascular endothelial growth factor (VEGF)-A and its receptor, VEGF-R2, play a central role in angiogenesis via various mechanisms. One of these pathways works in conjunction with a Rho (GTP binding protein)/Rho Kinase, whereby VEGF-A leads to an increase in endothelial (EC) permeability. In this pathway, VEGF enhances migration capability and promoting cytoskeletal modulations and stress fibre generation.15 Controlled inhibition of Rho/Rho Kinase via MAPK (ERK 1, 2) activation will decrease endothelial cell apoptosis and stimulate cellular sprouting, resulting in new blood vessel formation.16 According to Gupta and colleagues,17 in 1999, VEGF-A stimulation can augment angiogenesis via an additional pathway. Stimulation of VEGF-VEGFR-2 will promote phosphorylation of PI-3kinase and, subsequently, Akt resulting in inhibition of apoptosis and increased cell proliferation.18 In the same manner, VEGF can activate MAPK pathways via stimulating endothelial nitric oxide (eNO-NO) production19, where MAPK activation will decrease apoptosis and increase cell survival, by stimulating ERK1,2 and inhibit stress-activated protein kinase/c-jun-NH2-kinase(SAPK-JNK).20 The effects of opioids on blood vessel formation are highly contentious.

References


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Opioids stimulate angiogenesis

The wide use of opioids in daily practice, particularly in patients with malignancy, led many researchers to examine the relationship between opioids and new blood vessel formation; a vital component of tumour growth and metastasis. Many studies suggested that morphine can stimulate angiogenesis. Polakiewicz and colleagues, in 1998 showed that opioids can stimulate MAPK pathway (ERK 1,2)19 which could be mediated via activation of any of the four opioid receptors. Gupta and colleagues, 2006 (in separate studies) proposed that opioids have a VEGF-like role on angiogenesis. They found that MOP activation by morphine (MOP agonist) will activate both PI-3kinase and eNOS- secondary to Ras activation; ending with MAPK and Akt phosphorylation. This was in line with Macey and colleagues, in 2006 who found that ERK1, 2 could be stimulated by MOP agonists in murine striatal nerve cells. A similar mechanism was suggested by Leo and colleagues, 2009 who found that morphine can promote human umbilical vein endothelial cell (HUVEC) proliferation in vitro, to a level similar to that produced by VEGF. Moreover and according to Dai and colleagues23 24, endogenous opioid ligands show pro-angiogenic effects on both chick embryo and HUVEC cells. Other potential mechanisms have been suggested. Singleton and colleagues25, 2006 showed that morphine can increase endothelial cell migration and cellular proliferation in a methylnaltrexone (peripheral MOP antagonist) sensitive manner. The authors suggested that the mechanism was based on activation of Src tyrosine kinase with subsequent cross activation of VEGF-VEGFR-2-RhoA pathway.

Opioids inhibit angiogenesis

Intriguingly, not all studies report a stimulation of angiogenesis. Blebea and colleagues, 2000 reported that activation of opioid receptors, via endogenous opioid ligands, inhibited angiogenesis in chick chorioallantoic membranes. Although they did not elaborate a mechanism they confirmed the response was receptor-based, as opioid growth factor (met-encephalin) decreases numbers and length of blood vessels while naltrexone, a long-acting opioid antagonist, reversed these effects.26 Balasubramanian and colleagues27, 2001 found that morphine inhibits VEGF expression in hypoxic vascular endothelial cells and this action is reversed by naloxone treatment. Roy and colleagues28, 2003 showed that morphine inhibits both VEGF mRNA expression and protein production in murine cardiac myocytes. They proposed

![Diagram of possible mechanisms involved in opioid increased angiogenesis.](image-url)
that opioids activate MAPK/ERK (1, 2) which will down-regulate HIF-1α through inhibition of the Akt-PI-3kinase pathway. In an attempt to address the issues of pro vs anti angiogenic actions, several groups supporting the pro-angiogenic role of opioids, tried to explain the anti-angiogenic action of morphine based on dose/exposure; at high doses there is an anti (toxic) and low(er) doses pro angiogenic effect.18

Another possible mechanism involves the dual action of Rho/Rho kinase pathway. Initially, Rho/Rho kinase activation via VEGF-A/VEGFR-2 will facilitate cell migration, before a migratory down regulation under the influence of MAPK/ERK (1, 2) resulting in increased cell survival and EC sprouting. If MAPK/ERK (1, 2) activation occurs earlier, effectively inhibiting Rho/Rho kinase earlier, this may disrupt angiogenesis via decreasing cell migration. This could be dose and/or time related and further experimental work is warranted.

Conclusion

The story of opioids being bad for cancer survival is complex and hinges around three ‘pro-tumour’ actions; (1) cancer cell proliferation/migration, (2) immune depression and (3) angiogenesis. All three actions are contentious and interlinked. The effects of opioids on angiogenesis (or neovascularization) are particularly contentious with compelling data sets indicating both pro and anti-angiogenic actions. A definitive conclusion is hard to reach and this in line with Lee and colleagues19, 2014 in their review assessing the impacts of pain management on cancer patients. Opioid type and dose, and the underlying disease pathology and organ(s) involved are likely to be critical. We believe the pro-angiogenic (or neo-vasculogen) effects predominate (see Fig. 1). What is clear is that further systematic studies of different pro-angiogenic (or neo-vasculogenic) effects predominate (see Opioid type and dose, and the underlying disease pathology and sprouting during angiogenesis. Cancer Cell 2006; 9: 33–44


References


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Losing concentration: time for a new MAPP?

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Anaesthetic vapor analysis is an essential element of monitoring during inhalation general anaesthesia,¹ and recent publications have re-emphasized the importance of monitoring end-tidal anaesthetic concentrations as a means of minimizing the risks of awareness in this setting.²⁻⁴ Consequently, the question arises as to whether exhaled vapour concentration is a valid measure of the dose of volatile anaesthetic gases in all circumstances. More specifically, can such measures be misleading in conditions of altered barometric pressure that occur with increasing altitude? A quarter of the world’s population live at more than 500 m above sea level and nearly 10% reside higher than 1500 m,² many in highly populated cities, including Denver, CO, USA [at an altitude of 1500 m], or a calculated higher setting on the dial must be selected. At an altitude of 2000 m, the operator must manually increase the amount of a given gas dissolved in a liquid is directly proportional

because all variable bypass vaporizers deliver varying dilutions of saturated vapour pressure, and not a concentration⁵ (the desflurane vaporizer functions on a different principle). However, the fractional concentration will be dependent on the barometric pressure. Thus, a variable bypass vaporizer set to deliver 2% at sea level will deliver a partial pressure of 2 kPa regardless of the barometric pressure. The same vaporizer in Johannesburg or Denver, CO, USA [at an altitude of ~1700 m (5500 feet) and a barometric pressure of ~80 kPa] will continue to deliver the same partial pressure of 2 kPa, but at a concentration of 2.5%. At half of the sea-level barometric pressure (say ~5300 m), the concentrations will be double. Therefore, if the anaesthetist were to titrate anaesthetic agent dosage to end-tidal volatile concentration, the partial pressure would be half that delivered at sea level and the risk of underdosing (and in some circumstances accidental awareness under anaesthesia) would be substantial. Modifying the vaporizer to deliver the set concentration will almost certainly result in a significantly lower partial pressure of the agent being delivered. It is thus illogical to calibrate these instruments in terms of concentration. Importantly, the most widely used device for the factory calibration of vaporizers is the refractometer, a device that measures partial pressure, not concentration.

The physical concept underlying this proposal is beautifully illustrated by the classical teaching (and erstwhile common final fellowship question) about the degree to which an anaesthetist delivering volatile anaesthesia at altitude would need to alter the fractional concentration set on a variable bypass vaporizer in order to achieve the same level of anaesthesia as at sea level. The answer to this thought experiment is that the same settings as at sea level will result in the same proportion of the saturated vapour pressure of that volatile and therefore the same partial pressure and pharmacological effect at any altitude (although this theoretical degree of precision is not entirely accurate because alterations in flow splitting ratios with changes in barometric pressure may have minor, unpredictable effects; see http://www.openanesthesia.org/vaporizer_output_at_altitude/). This is because all variable bypass vaporizers deliver varying dilutions of saturated vapour pressure, and not a concentration⁵ (the desflurane vaporizer functions on a different principle). However, the fractional concentration will be dependent on the barometric pressure. Thus, a variable bypass vaporizer set to deliver 2% at sea level will deliver a partial pressure of 2 kPa regardless of the barometric pressure. The same vaporizer in Johannesburg or Denver, CO, USA [at an altitude of ~1700 m (5500 feet) and a barometric pressure of ~80 kPa] will continue to deliver the same partial pressure of 2 kPa, but at a concentration of 2.5%. At half of the sea-level barometric pressure (say ~5300 m), the concentrations will be double. Therefore, if the anaesthetist were to titrate anaesthetic agent dosage to end-tidal volatile concentration, the partial pressure would be half that delivered at sea level and the risk of underdosing (and in some circumstances accidental awareness under anaesthesia) would be substantial. Modifying the vaporizer to deliver the set concentration will almost certainly result in a significantly lower partial pressure of the agent being delivered. It is thus illogical to calibrate these instruments in terms of concentration. Importantly, the most widely used device for the factory calibration of vaporizers is the refractometer, a device that measures partial pressure, not concentration.

The exception to this principle, the desflurane vaporizer, features dual circuits that function by blending gas and vapour and behaves much like a nitrous oxide cylinder, delivering a volume of vapour that will expand on exposure to reduced barometric pressure. This vaporizer will either need to be recalibrated at altitude to ensure that the appropriate partial pressure is delivered or a calculated higher setting on the dial must be selected. At an altitude of 2000 m, the operator must manually increase the concentration control dial from 10 to 12.8% to maintain the required anaesthetic partial pressure.⁶

Henry’s law states that, at a constant temperature, the amount of a given gas dissolved in a liquid is directly proportional
