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REVIEW ARTICLE

Opioids and cancer survival: are we looking in the wrong place?

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Abstract

There is a controversial narrative in the anaesthetic literature suggesting that anaesthetic technique (including opioids) may be detrimental to survival after tumour resection. The initial observations were retrospective. Several prospective studies are ongoing; one in breast cancer has reported no adverse outcome. The evidence for an effect of opioids stems from three pieces of information: (1) opioids depress the immune system, (2) opioids potentially promote angiogenesis, and (3) opioids potentially support tumour growth. Although the evidence for (2)/(3) is unclear, combinations of these effects are beneficial to tumours and potentially promote metastatic reseeding. Accepted wisdom suggests that opioid effects are driven by opioid receptor activation but the presence of opioid receptors on immune cells for example is unlikely. Immune cells, vascular endothelium and a range of tumour cells express Toll-like receptor 4 (TLR4) receptors (for Gram-negative bacterial wall components), and there is growing evidence for opioids interacting with this alternative receptor; and for some there is paradoxical naloxone sensitivity. Is the focus on opioid receptors and cancer the wrong target? TLR4 receptor activation produces immune activation, stimulates angiogenesis, and supports tumour survival. We know that some opioids are more immune suppressive than others (there is no such comparative information for angiogenesis and tumour survival); this may correlate with TLR4 activation. If there are clusters of opioids that have more opioid than TLR4 profiles and *vice versa*, this may influence outcome. If this is the case, then evidence-based advice could be given for perioperative use in the oncology—anaesthesia setting.

Keywords: angiogenesis; cancer; immune function; opioids; TLR4 receptors

Cancer Research UK 2015—7 state, '*there are around 367,000 new cancer cases in the UK every year; ~1,000 every day*'; '*breast, prostate, lung and bowel cancers together accounted for more than half (53%) of all new cancer cases in the UK in 2017*'.[1] Analysis of predictions from Maddams and colleagues[2] underscores the growing nature of the problem with ~2.9 million people living with cancer in 2020, which is expected to increase to ~4.0 million in 2030. Surgery remains at the centre of cancer treatment. Cancer Research UK statistics indicate that 45% of cancer patients will undergo surgery,[1] equating to ~165 000 surgical procedures per year. Recurrence is an important issue to consider and depends on tumour type and stage at diagnosis. With every surgical procedure, there will be an anaesthetic which is an excellent example of polypharmacology with a wide range of agents in use. These include — but are not limited to — sedatives, neuromuscular blocking agents, volatile and intravenous anaesthetic agents, and analgesics such as opioids; these are used in variable combinations.

Opioids interact with naloxone sensitive μ (MOP), δ (DOP), and κ (KOP) or naloxone insensitive nociceptin/orphanin FQ (N/OFQ; NOP) G-protein coupled receptors. N/OFQ is the endogenous ligand for NOP. All opioid receptors can support analgesia, but the main clinical target is MOP with growing interest in drugs for NOP.[3,4] Moreover, there is strong evidence that non-selective mixed opioids can offer high-quality analgesia with reduced side-effects; this is driving some drug development programmes.[5] Opioids are known to be immune depressant but the site of action is controversial[6–8]; they also variably affect angiogenesis[9,10] and tumour growth and biology.[11,12] This combination of actions could be defined as pro-tumour and is particularly relevant in the perioperative period.

An important paper published in 2006[13] suggested that some anaesthetic drugs might worsen clinical outcome from breast cancer surgery. This was seen with a volatile-based general anaesthetic when compared with a regional anaesthetic technique and has been shown for other tumours.[14,15] The gold standard to test an association is a prospective interventional clinical trial: although some clinical trials are ongoing, most have yet to report (see Cata and colleagues[15]). One trial (NCT00418457), also conducted in patients with breast cancer, indicated the association not to be present.[16] In correspondence one of the authors states 'Although our data indicate that regional anaesthesia is unlikely to affect breast cancer outcome, we await ongoing and emerging RCT results evaluating other anaesthetic techniques and in different tumours'.[17] It is suggested from these data that opioids are not pro-tumour. However, opioids are used as part of a mixed anaesthetic. The opioid used was fentanyl (and intraoperative morphine), so there are limited data for other opioids and the range of tumours routinely presenting for resection. Lucia and colleagues[18] recently performed a systematic review of opioids and breast cancer recurrence, in which they concluded that the controversial evidence set leaves the issue unresolved. To add to the controversy, there are some recent elegant genomic data in breast[12] and renal tumours[19] to suggest that opioid agonists may be detrimental to tumours. This counter-view plays to retrospective data in laryngeal carcinoma where higher tumour MOP expression correlates with improved survival.[11] The picture with respect to opioids and cancer biology mechanistics is as controversial now as it was in 2006.

Opioids/toll-like receptor 4 and immune suppression

In 1950 Hussey and Katz[20] first linked infection to narcotic abuse. Consensus suggests three sites of interaction — (1) the immune cell, (2) the hypothalamic—pituitary—adrenal (HPA) axis, or (3) via central actions — and we have reviewed these topics.[6] In particular, expression of MOP receptors on peripheral immune cells and often alongside naloxone sensitivity is reported but is controversial.[6] A recent article by Karagiannis and colleagues,[21] using single-cell RNA sequencing (scRNA-seq), showed that chronic opioid usage led to widespread suppression of the antiviral gene programme in multiple immune cell types, when challenged by lipopolysaccharide (LPS). More interestingly, the same suppression was seen *in vitro* with morphine treatment. Although scRNA-seq was unable to detect any opioid receptor mRNA, population-level RNA-seq revealed MOP mRNA in some T cells, monocytes, and natural killer (NK) cells, but not in B cells, whereas DOP and KOP mRNA expression is very low or undetectable. NOP receptor mRNA was present in all immune cell types, with highest levels in monocytes.[21] We have never been able to detect mRNA for MOP/DOP/KOP; we have consistently determined mRNA for NOP, and in a recent study with a new fluorescent NOP probe N/OFQ$_{ATTO594}$ we also report receptor protein.[22−25] Recent unpublished data (in sepsis) from our laboratory with N/OFQ$_{ATTO594}$ has identified the presence of NOP receptor protein on both B cells and T cells, with T cells requiring pre-treatment with LPS/peptidoglycan G (PepG). Consistent with mRNA and protein, NOP activation has functional consequences, for example in migration (see Al-Hashimi and colleagues[6] and Sacerdote[7]). HPA axis activation has the potential to affect immune function via a steroid-driven action; the evidence for such an interaction is poor with

variation dependent on species studied and route of opioid administration.[6] Clinical data are lacking. An example that crosses central-peripheral sites uses NK cells. In rats, morphine injected into the periaqueductal grey (brain) decreased splenic NK cell activity. This was not seen with a morphine derivative that does not cross the blood—brain barrier.[26] In a different study, buprenorphine, a mixed opioid partial agonist, failed to mimic the effects of morphine in inhibiting NK cell activity.[27] In human volunteer blood studied 2 and 24 h after i.v. morphine, a similar depression in peripheral NK activity is seen.[28] If there is no or variable low opioid receptor expression on immune cells what is the proposed target? A role for Toll-like receptor 4 (TLR4) receptors in immune function and signalling is well known; these are cell specific and cause activation[29,30]; what is less well known outside the opioid field is opioid—TLR4 interaction.

TLR4 receptors recognise pathogen-associated molecular patterns, specifically LPS in the cell wall of Gram-negative bacteria.[31] The TLR4 receptor is expressed in a number of cell types; relevant to this review is immune — but also vascular endothelial and cancer — cells. In infection or potentially when bound with opioids, LPS (bound to LPS binding protein) is transferred to cluster of differentiation 14 (CD14), which then binds to myeloid differentiation factor 2 (MD2) protein; this causes TLR4 dimerisation and activation. There are two activation pathways: myeloid differentiation primary response 88 (MyD88) dependent and independent; the former activates mitogen-activated protein kinase (MAPK) and nuclear factor kappa light chain enhancer of activated B cells (NF-κB).[31]

Hutchinson and colleagues[32,33] (in human embryonic kidney [HEK] cells expressing TLR4) showed that morphine, methadone, levorphanol, dextrorphan, oxycodone, pethidine, buprenorphine, and fentanyl activated TLR4. The response to morphine was even reversed by naloxone. For immune modulation, not all opioids are the same and there is evidence for opioid metabolites having TLR4 activity. Indeed, Lewis and colleagues[34] showed that the major morphine metabolite morphine-3-glucuronide (M3G) (no activity at opioid receptors) activates TLR4 and also upregulated TLR4 receptor mRNA expression in the spinal cord of rats. This agreed with data from Hutchinson and colleagues,[32] where naloxone sensitivity was also demonstrated. In the clinic morphine and fentanyl display a high degree of immune modulation; tramadol and buprenorphine have weak or no immune modulation. There are limited data for NOP ligands and no data for the mixed compounds such as cebranopadol[35] and the putative (but questioned[36,37]) biased agonist oliceridine[38] (Fig. 1).

Opioids/TLR4 and angiogenesis

In response to angiogenic stimuli (e.g. vascular endothelial growth factor [VEGF]), vessel extracellular matrix (ECM) is degraded, and vascular endothelial cells differentiate into tip cells and migrate towards the stimulus, forming tubes (new vessels). In adjacent areas of sprouting, vascular fusion produces a connecting lumen.[39] The effects of opioids on angiogenesis is controversial: stimulatory and inhibitory actions have been reported and summarised.[9,10] It has been proposed that in endothelial cells, tumour-derived VEGF increases MOP expression and morphine stimulates MOP signalling pathways leading to cell proliferation and vessel formation; naloxone sensitivity is not seen.[40] There are some highly contradictory *in vivo* animal data. Gupta and colleagues[41] reported a naloxone-insensitive angiogenic response to morphine in mice. Bimonte and colleagues[42] also reported a naloxone-
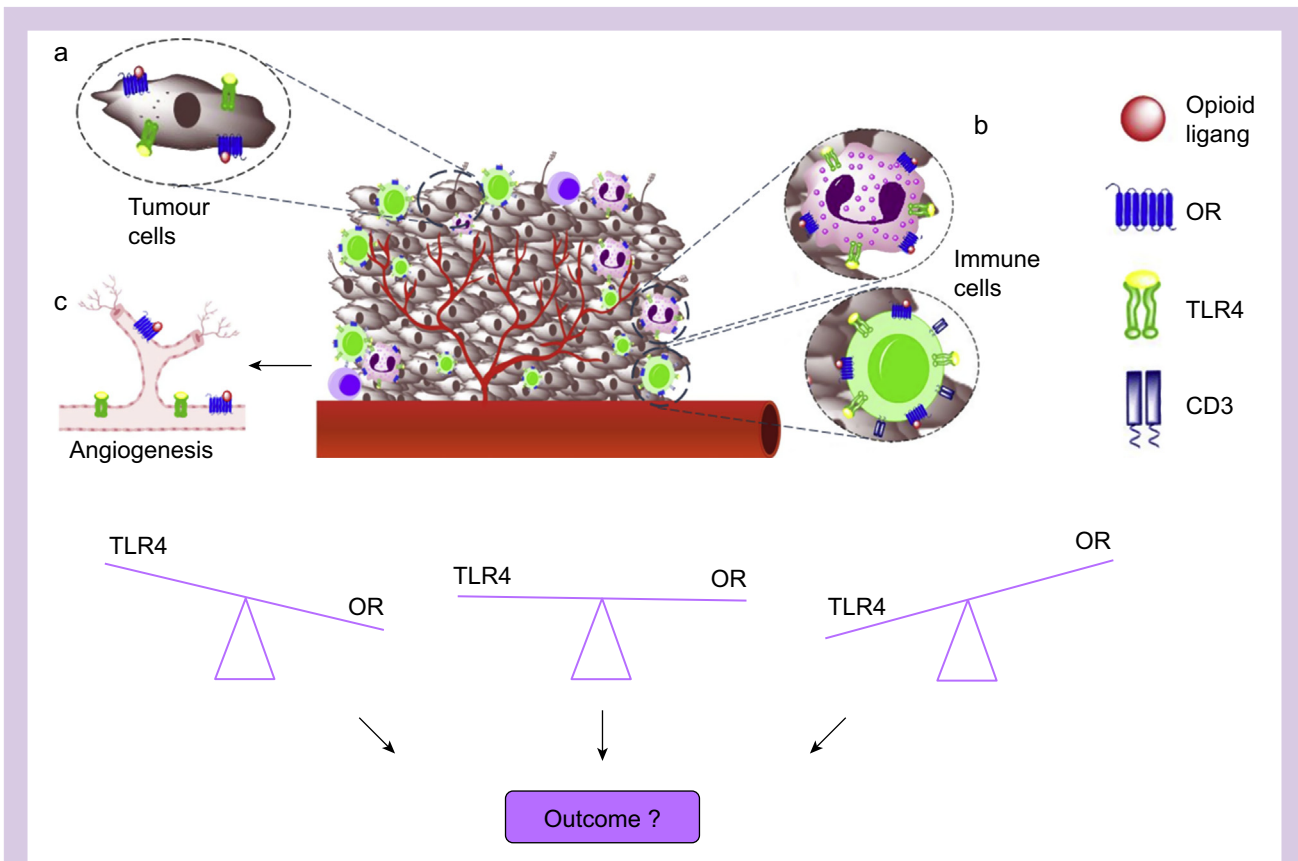
Fig 1. Opioid and TLR4 receptors are variously expressed in tumour, immune, and vascular cells. There is controversial evidence that these receptors individually support tumour growth (a); modulate immune function; mononuclear, and polymorphonuclear cells (b); and stimulate angiogenesis (c). A potential interaction between opioid and TLR4 receptors has been suggested but the profile(s)/relative balance of this interaction (scales in the lower part of the figure) on final outcome are unknown. CD3, cluster of differentiation 3; OR, opioid receptor; TLR4, Toll-like receptor 4.

insensitive morphine angiogenic response; naloxone did reverse the morphine increase in tumour size; was this a TLR4 response? Nguyen and colleagues[43] demonstrated angiogenesis and lymphangiogenesis in mice; there does not appear to be naloxone sensitivity. Morphine-driven angiogenesis was absent in mice where the MOP receptor has been knocked out.[44] It is important to underscore that there are studies showing reduced angiogenesis.[45-47] Receptors for TLR are variably expressed in the vascular tree where they are involved in angiogenesis and TLR4 are expressed in human umbilical vein endothelial cells (HUVECs)[48] and on microvascular endothelial cells.[39] TLR activation promotes ECM degradation via matrix metalloproteinase expression, driven by extracellular signal-regulated kinase 1/2 (ERK1/2) and NF-κB. TLR4 activation is also linked to increased (direct and indirect; via hypoxia-inducible factor [HIF]) levels of VEGF-A[39] (Fig. 1). Unlike the clinical situation described above for opioid immune suppression, no comparative information on opioid drugs exists for angiogenesis.

Opioids/TLR4 and tumour growth

Where opioid receptors are expressed, activation can have variable effects on tumour activity. There are reports in a variety of cell types of increased apoptotic activity[49-51] but also of growth and metastatic potential.[52] Singleton and colleagues[53] demonstrated that lung cancer biopsies expressed MOP and suggested a link between MOP expression and tumour progression. This study widens the findings in a xenograft model showing that lung tumour MOP overexpression supports growth and metastasis.[52] TLR4 receptors are expressed in tumour cells and have a role in tumour biology. Mokhtari and colleagues[54] have recently reviewed the expression of TLR receptors in a range of tumours and indicate that TLR4 is expressed in breast, lung, neuroblastoma, and colorectal neoplasms. Expression of TLR4 and opioid receptors creates the potential for crosstalk, structural interaction, and a substrate for opioid modulation of activity (Fig. 1). Again, unlike the clinical situation for immune suppression, no such comparative information exists for direct tumour effects of opioids.

Linking opioid-TLR4 signalling functional responses

Depending on the tissue, opioid receptors open K^+ and close Ca^{2+} channels reducing pain neurotransmission. Opioid

receptor activation also reduces 3′,5′-cyclic adenosine monophosphate (cAMP) and variably activates MAPK,[4] and there is some evidence for actions at NF-κB.[55] In terms of crosstalk with pain pathways, TLR4 receptors are implicated in the induction of neuropathic pain and acute−chronic pain conversion.[56] Interaction between opioid and TLR4 signalling is suggested in analgesia, immune function, gastrointestinal motility,[57] and addiction.[58] Indeed, opioids bind to MD2.[32] Shah and colleagues[59] suggest that morphine binding switches MD2 to its active conformation that gains stability on TLR4 interaction. Naloxone switches MD2 conformation to its inactive state. Tumour microenvironment mimics that seen in chronic inflammation and damage-associated molecular patterns (DAMP) from necrotic tumour tissues create a TLR4 activation signal.[60,61]

What does all of this mean for the opioids and cancer story?

With respect to immune suppression, angiogenesis, and tumour growth, are there differences between opioids? Differences with respect to immune modulation are known, even if the site of action is not definitively known. With respect to cancer survival, are opioid receptors the appropriate targets to focus on? Is the TLR4 receptor a critical target and is relative activity at TLR4 *vs* opioid receptors important? Opioids are immune suppressive but TLR4 receptors support immune activation. If there are differences in opioid and TLR4 activation profiles, do some opioids cluster towards TLR4 receptors rather than opioid receptors for example? Does this predict outcome? A full comparative profile of opioid action at opioid and TLR4 receptors in models of angiogenesis and tumour survival is required. We are currently in a position where retrospective studies suggest an adverse link, and prospective studies are beginning to report but the jury remains out. The full range of opioids at clinically achievable concentrations remains to be studied particularly in models of angiogenesis and tumour growth. If overall relative propensity of opioids to be pro-tumour or anti-tumour can be predicted then more rational clinical use can be suggested. This has to be good for our patients.

In a recently published study Sun et al[62] examined the effects of opioids on cancer survival in patients with chronic pain. The authors selected 1716 patients from the Taiwan Cancer Registry Database; 268 patients with chronic pain who were prescribed ≥180 defined daily doses of opioid were compared with 1430 patients with chronic pain who were prescribed ≤28 defined daily doses of opioid. The adjusted hazards ratio for overall survival with long term use of opioids was 3.53 (poorer overall survival). This data suggests long term opioid use might be associated with poor outcome. This is a small study with uneven matching.

Authors' contributions

All authors were involved in writing, review, and approval of the final version of the manuscript.

Declaration of interest

DGL is chair of the board of *British Journal of Anaesthesia* and scientific adviser to Cellomatics, a SME-CRO. None of the remaining authors have conflicts to declare.

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