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Cancer pain: mechanisms based personalized analgesia

M. Vlaskovska[1], S. Surcheva[1] & L. Kasakov[2]
[1]Department of Pharmacology and Toxicology, Medical Faculty, Medical University Sofia, 1431 Sofia, Bulgaria and [2]Institute of Neurobiology, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

The International Association for Study of Pain (IASP) has launched Global Year against Cancer Pain which runs from October 2008 through October 2009. Efforts are centred to educate health-care providers, governments and the public on the pain and suffering experienced by people with cancer [IASP Newsletter (4), December 2008]. More than 10 million people are diagnosed with cancer each year and it is estimated that by 2020 this would increase to 15 million new cases each year (Stewart & Kleihues, World Cancer Report, 2003). Cancer-associated pain can be present at any time during the course of the disease, but the frequency and intensity of cancer pain tend to increase with advancing stages of disease. Between 75 and 90% of patients with metastatic or advanced-stage cancer will experience significant cancer-induced pain (Meuser *et al.*, 2001). Despite the increasing prevalence of cancer, improvement in the detection and treatment (aggressive chemotherapy) of most types of cancer has resulted in a significant increase in survival rates (Eduards *et al.*, 2005). Given the increasing life span of cancer patients, new mechanism-based therapies need to be developed to reduce cancer-related pain.

Until recently the management of cancer pain has been largely empirical (Mantyh, 2006a). The World Health Organisation (WHO) has promoted the three-step analgesic ladder as a framework for the rational use of analgesics in the treatment of cancer pain (Cancer Pain Relief. WHO, Geneva; 1986, 1996). Step I specifies the use of non-opioid analgesics (paracetamol, non-steroidal anti-inflammatory drugs) for the treatment of mild pain; step II recommends weak opioids (codeine, tramadol, etc) with or without non-opioids, for moderate pain; and step III comprises strong opioids with or without non-opioids for strong pain. If needed adjuvant drugs can be used at each step. Despite the general conclusion that the WHO method has been of enormous benefit for the treatment of cancer pain worldwide (Eisenberg *et al.*, 2005) it has been shown that the rate of pain relief in patients with advanced cancer is as low as 50% (Murakawa *et al.*, 2007). Although there are various reasons for this poor improvement of the rate of pain relief, the leading factors are inadequate (relatively low) doses of opioids used, the mechanisms of cancer pain and the genetic determinants of the patients (Riley *et al.*, 2007). Both medical doctors and patients are concerned about the adverse effects of opioid and non-opioid analgesics chronically used. In the case of opioids major concerns are development of tolerance to analgesic activity and withdrawal reaction (physical dependence). With the development of tolerance the dose of opioid is increased in order to achieve analgesia which increases the risks of toxic/adverse (vomiting, constipation, somnolence, pruritus, myoclonus, delirium, blurred vision, etc.) effects from opioids. Long-term side effects are abnormal pain sensitivity, hypogonadism (testosterone or estrogen replacement needed) and immunosuppression. Increased pain sensitivity is observed not only during opioid withdrawal, but new evidence suggests that increased pain sensitivity can also occur during opioid administration. Interestingly, the cellular mechanisms of opioid-induced hyperalgesia have much in common with those of neuropathic pain and opioid tolerance, including glutamatergic mechanisms (Mao, J., 2008). Our results have suggested that NMDA antagonists or/and opioid rotation/switching might be useful to alleviate opioid-induced hyperalgesia (Vlaskovska *et al.*, 1997).

Recently a five-step pain and side effect ladder is proposed (Riley *et al.*, 2007). The proposed 4th step involves "opioid switching" and includes both pain and side effects as criteria for switching analgesics. Interestingly 3 out of 4 factors predicting need to switch to other opioid are adverse effects of analgesics used. Finally, if switching opioids fails, it is proposed that the 5th and final step of WHO analgesic ladder should involve anaesthetic intervention.

Different new formulations of opioids are introduced to cope breakthrough pain in cancer patients. Breakthrough pain is a transient flare-up pain superimposed on an otherwise stable pain pattern in patients treated with opioids. It is normally severe in intensity with a rapid onset and variable duration. Breakthrough pain is considered a negative prognostic factor (Mercadante, S., 2006). Patients with untreated breakthrough pain have greater levels of anxiety and depression and are less satisfied with their opioid therapy. Use of antidepressants and anxiolytics might be helpful.

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In order to optimize analgesic efficacy, to lower adverse effects and to optimize dosing, emphasis shifts to clinical genomics, gender/sex and psychosocial issues (Bernardes *et al*,. 2008), which play significant role in analgesic and adverse effects of opioids, non-opioid analgesics (NSAID) and psychotropic drugs (anticonvulsants, antidepressants, benzodiazepines) which are used to treat cancer pain. Experimental and clinical data showed that expression polymorphism in CYP2D6 (codeine, tramadol, 5-HT3 antagonists, tricyclic antidepressants, etc.), CYP2C19 (diazepam, omeprazole) and CYP2C9 (NSAID, warfarin) could result in lack or decreased analgesic activity, sedation or increased risk of gastrointestinal bleeding (Gardiner & Begg, 2006). The A118G polymorphism of the μ-opioid receptor has been shown to change the analgesic potency of morphine and morphine-6 glucorunide. The analgesic and toxic doses of opioids differ significantly in patients with polymorphism of the enzyme COMT and melanocortine receptors (MC1R) (Reyes-Gibby *et al.*, 2007). It should be also stressed that experimental, clinical and epidemiological studies have shown that women experience and report experiencing more pain than men. Women suffer more from migraine, rheumatoid arthritis and visceral pains from non-sex specific organs that share at least part of their central sensory projection with the reproductive area like irritable bowel syndrome, pain from the urinary system etc. The analgesic effect of k-agonists is much stronger in women with two inactive variance of MC1R allele. Sex steroid hormones influence not only the sensitivity of peripheral sensory neurons but also development of central sensitization or pain memory, stress, anxiety and motivation (Nashar *et al.*, 2006). The role of sex steroid hormones is very important in cancer pain and analgesia, since hormone sensitive tumours are often treated with drugs affecting the levels of estradiol/testosterone.

The primary goal of preclinical and clinical studies is to provide insight into the mechanisms that drive or mask cancer pain, the mechanisms by which anti-neoplastic agents induce peripheral neuropathy, as well as to study the specific mechanisms of visceral and bone (cancer) pain, the influence of sexual hormones and genetic variants on different types of pain and on the effects of analgesics used. Considering most of the factors mentioned medical doctors would be able to apply new mechanism-based analgesic therapies for alleviation of cancer pain.

Cancer pain can arise from different processes, either by direct tumour infiltration/involvement, as a result of diagnostic or therapeutic surgical procedures (such as biopsies and resection), or as a side effect of toxicity related to therapies used to treat cancer (chemotherapy and radiation therapy). The pathophysiology of cancer pain comprises of various types of pain: nociceptive/inflammatory hyperalgesia (tumour infiltration, surgical procedures, inflammation etc), neuropathic pain (traumatic and toxic destructions of sensory nerves), visceral pain (colorectal or hollow tube sack organs distension) and psychogenic (disease progression and toxic effects of the tumour and anticancer drugs).

Development of experimental models of cancer pain, revealed that tumour cells produce large amounts of PGs, endothelins, ATP, activating $P2X_3$ purinoceptors as well as bradykinin, interleukins, epidermal growth factor, transforming growth factor etc. (Mantyh, P., 2006b), which activate specific receptors/nociceptors. It is well known that PGs potentiate more than 40 fold the nociceptive and pro-inflammatory effects of the mentioned mediators. Several tumour cells and tumour-associated macrophages express high levels of COX2, which produce PGs involved not only in pain and inflammation, but also in tumour cell growth and metastasis, as they inhibit prostacyclin and angiogenesis. Therefore, COX2 inhibitors (celecoxib, etoricoxib, valdecoxib, parecoxib, lumiracoxib) might be successfully used not only as analgesics in bone and inflammatory pain, but also to suppress tumour growth and metastases. However, the same mechanism of action causes risks from thrombosis, which is a serious adverse effect of coxibes.

Tumour cells become ischaemic and undergo apoptosis as the tumour burden exceeds its vascular supply, which results in local acidosis. The two major classes of acid-sensing channels expressed by nociceptors are TRPV1 and ASIC-3 and transmit pain due to low pH and heat. Tumour-induced release of protons and acidosis may be particularly important in the generation of bone cancer pain. Recent work has shown that osteoprotegerin and bisphosphonate, both of which are known to induce osteoclast apoptosis, are effective in decreasing osteoclast-induced bone cancer pain. TRPV1 and ASIC antagonists (AZD1386) are in phase II clinical trial and may be used to reduce bone cancer pain by blocking acid-sensitive channels. Interestingly the metabolite of paracetamol N-acetylphenolamine interacts with TRPV1 receptors, which might be connected to its analgesic activity.

Another very important aspect of cancer pain is the mechanism of peripheral neuropathy induced by anticancer drugs and mechanisms of central sensitization due to tumour growth and destruction of the sensory nerves. Data are accumulating for the specific changes in DRG by paclitaxel and other anticancer drugs, which lead to typical neuropathic pain. In the cases of neuropathic changes, a better analgesic effect

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could be observed with pregabalin and other anticonvulsants that specifically block the overexpressed Na^+ or Ca^{2+} channels in sensory ganglia.

Tumour cells release high concentrations of ATP, which is a major sensory transmitter. We showed that purinergic transmission is involved in various mechanisms/types of cancer pain (visceral, inflammatory, and neuropathic). Nociceptors are densely supplied with $P2X_3$ and $P2X_{2/3}$ receptors activated by ATP, which is released from the cells due to damage, inflammation, hypoxia or distension/constriction. ATP can also be released from sympathetic nerves, endothelia and tumour cells. In the spinal cord the receptors are localized presynaptically, which activation by ATP released upon the incoming peripheral noxious stimulation facilitates glutamate release or postsynaptically secondary sensory neurons, which evoked excitation. Spinal interneurons releasing ATP as a fast transmitter co-secrete the inhibitory transmitter GABA and vice versa - GABA releasing interneurons co-secrete ATP, which suggests that spinal GABAergic interneurons could be source of synaptic ATP. $P2X_3$ receptors contribute to heat induced pain as they are co-localized with vanilloid $TPVR_1$ receptors.

Acute pain It is known that exogenous administration of P2X agonists evokes acute nocifensive responses. However, the release of ATP and activation of $P2X_3$ and $P2X_{2/3}$ receptors play a secondary role in the physiological nociception where other algogenic substances are more important for the induction of acute pain. It is plausible to speculate that $P2X_3$ receptors contribute substantially to the acute pain induced by tissue damage, which is often the case in cancer pain.

Inflammatory pain The sensitivity of P2X receptors augments in the presence of inflammatory mediators (PGE2, bradykinin, substance P, histamine, 5-HT) and/or tissue acidosis and vice versa the inflammation is intensified by ATP.

Visceral pain: The submucous plexuses of most visceral organs contain $P2X_3$ and $P2X_{2/3}$ positive afferents. During distension of the wall of tube or sack viscera ATP is secreted from epithelial cells and diffusing in the vicinity may activate the purinergic receptors of low threshold intrinsic sensory nerves thus contributing to peristaltic reflexes. If excessive distension occurs higher amount of ATP is released from epithelial cells, which activates $P2X_3$ and $P2X_{2/3}$ receptors of high-threshold extrinsic sensory afferents thus exciting the pain related nerve structures (Vlaskovska et al., 2001). Interestingly Metamizole (analgin) was found to suppress sensory nerve firing upon distension of urinary bladder. These data showed that part of analgesic activity of Metamizol in visceral pain due to distension (tumour, gall bladder stones, etc) might be due to interference with purinergic receptors.

Neuropathic pain: $P2X_3$ and $P2X_{2/3}$ receptors up-regulation, resulting in hypersensitivity at the site of nerve injury, is a likely component of the multi-etiological pathogenic mechanisms of neuropathic pain. Another purinergic component of neuropathic pain pathogenesis could be the co-release of ATP from postganglionic sympathetic neurons of dorsal root ganglia.

Pharmacological basis for analgesic drug development: The ubiquity of purinergic transmission and the major role of P2X purinoceptors in nociception necessitate the development of selective P2X antagonists. The invention of potent, non-toxic $P2X_3$ antagonists would pave the way for development of new analgesic drugs. However, this mission is not jet completed. Advancement has been made recently with the introduction of 2, 3'-O-(2', 4' 6')-trinitrophenyl-ATP (TNP-ATP) and pyridoxal-phosphate-6-azophenyl-2', 4'-disulphonate (PPADS) as specific antagonists of $P2X_3$ and $P2X_1$ receptors and 8, 8'-[carbonyl-bis-(imino-3, 1-phenylene-carbonylimino)-bis-(1, 3, 5-naphthalenetrisulfonic acid)] (NF023) as specific antagonist of $P2X_1$ receptors. Together with nicotinic acetylcholinergic and glutamatergic receptor superfamilies P2X purinergic receptors are the third class of ligand-gated ion channels. Local anesthetics, dizolcipine, phencyclidine, d-tubocurarine and other ion channel blockers could be useful for design of specific P2X antagonists with therapeutic potential.

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