European Journal of Pain 14 (2010) 781–783

Contents lists available at ScienceDirect

European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Editorial

Tapentadol and its two mechanisms of action: Is there a new pharmacological class of centrally-acting analgesics on the horizon?

Introduction

Tapentadol is a novel centrally-acting analgesic, that exerts its analgesic effects through μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI). In this issue of EJP, Schröder et al. describe the differential contribution of μ-opioid and noradrenergic mechanisms to the antinociceptive and antihyperalgesic efficacy of tapentadol in rat models of nociceptive and neuropathic pain. In June 2009, an international group of experts in neuropharmacology and pain research met to discuss the roles of these two important mechanisms in the processing of pain, and the importance of their pharmacological modulation for analgesia. During the discussion of the pharmacological profile of tapentadol it became obvious that apparently there are differences between tapentadol and other centrally-acting drugs and the suggestion was made to consider tapentadol a representative of a new pharmacological class of drugs, the MOR-NRI (μ-opioid receptor agonist noradrenaline reuptake inhibitor).

1. Pain mechanisms and pharmacological treatment

1.1. Pain transmission systems

In the ascending pain system, action potentials from Aδ or C nociceptors are relayed to second and third order neurons in the dorsal horn of the spinal cord. These projection neurons form an important component of the ascending pain transmission pathways through which the excitatory signal resulting from the noxious stimulus is sent to regions of the brain involved in the sensory components of pain. There are also parallel projections to limbic areas where the affective component of pain is generated.

A descending transmission system enables the cortex and subcortical areas to modulate pain signals at anatomically lower, mainly spinal levels. Responses are sent via the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM) to the dorsal horn. Here, neurotransmitters such as endogenous opioids, noradrenaline (NA) and serotonin (5-hydroxytryptamine, 5-HT) are released and bind to presynaptic receptors on the primary afferent fibers and to postsynaptic receptors on spinal cord transmission neurons to modulate the flow of noxious information. The effect of this 'top-down' modulation can be bidirectional, inhibitory or facilitatory (see e.g. Bannister et al., 2009).

1.2. Neuropathic pain

In neuropathic pain, the nervous system demonstrates remarkable plasticity that can result in pain without external stimuli (spontaneous pain) or in a disproportionately large response to a given stimulus (allodynia or hyperalgesia). One pathological mechanism involved is the development of sensitisation at a spinal and higher level. This results in greater excitability and a lower threshold in parts of the ascending pain transmission system.

Neuropathic pain occurs in conditions such as diabetic peripheral neuropathy, postherpetic neuralgia and radiating low back pain. Current medications for treating neuropathic pain include opioids, anticonvulsants, tricyclic antidepressants, mixed serotonin and noradrenaline reuptake inhibitors (SNRI), gabapentin and pregabalin. However, due to significant side effects, most of these agents have limited efficacy at tolerable doses.

1.3. Monoamine systems in pain

Noxious stimuli reaching the limbic brain can produce both inhibition and facilitation of spinal pain processing via the "on" and "off" cells in the RVM that play a pivotal role in the descending transmission system (Bannister et al., 2009).

The descending noradrenergic pathway promotes inhibition. Painful inputs into limbic areas can feed back via the PAG and RVM to the locus coerulus, which causes the release of NA at the spinal level, where it binds to α2 adrenoceptors. The descending serotonergic pathway can inhibit or facilitate pain via different 5-HT receptor subtypes. With respect to mechanical stimuli, it has been shown that under normal conditions there is continuing inhibition via the descending transmission system and α2 adrenoceptors. After nerve injury, net descending facilitation is enhanced (Suzuki et al., 2004). Thus, it is not surprising that selective serotonin reuptake inhibitors (SSRIs) are largely ineffective in the treatment of chronic pain because they indirectly produce concomitant activation of inhibitory as well as excitatory 5-HT receptors.

1.4. Opioids – mechanism of action

Opioids produce analgesia by binding to opioid receptors in the central nervous system. These receptors are inhibitory, as their activation hyperpolarizes neurons and reduces transmitter release. In the dorsal horn of the spinal cord, opioids interrupt the

1090-3801/$36.00
doi:10.1016/j.ejpain.2010.06.017

transmission of pain signals from incoming fibers by their presynaptic inhibitory actions and also reduce spinal neuronal activity through postsynaptic receptors. At the supra-spinal level, "off" cells in the RVM are indirectly activated (through opioid inhibition of inhibitory interneurons) and "on" cells are directly inhibited. This shifts descending controls towards an inhibitory influence, which synergises with the direct inhibitory actions of opioids at the spinal level.

Animal studies have shown that in the presynaptic neurons of the spinal dorsal horn, which bear approximately 75% of the spinal μ-opioid receptors (MOR), the expression of these receptors is reduced following nerve injury. Also, ectopic discharges are observed primarily in large diameter Aβ fibers and these may contribute to the development of allodynia. Unlike impulses conducted by C fibers, however, these afferent signals are not controlled by MOR agonists, and therefore spinal morphine, for example, is less potent in blocking allodynia caused by nerve injury, and spinal/supraspinal synergy is partly lost in neuropathic pain. Furthermore, since it has been shown that neuropathic pain is maintained by descending pain facilitation from the RVM, supraspinal opioid actions may be countered by changes in brainstem circuitry (Bannister et al., 2009; Millan, 2002; Ossipov et al., 2000; Przewlocki and Przewlocka, 2005).

2. Towards a new class of μ-opioid receptor agonist and noradrenaline reuptake inhibitor

The analgesic mechanisms of MOR agonism and NA reuptake inhibition (NRI) represent complementary modes of action. As discussed before, MOR agonism seems to be highly effective against acute nociceptive pain, but less suited to influence chronic neuropathic pain states, while NRI may be better suited for the treatment of chronic pain.

The novel, centrally-acting analgesic tapentadol offers the two mechanisms of action in the very same single molecule. The resulting effect is not only to provide effective analgesia for a broad range of acute and chronic pain conditions, but also to achieve an 'opioid-sparing' effect, i.e. to lower the dose of tapentadol required to produce a given level of analgesia thanks to the contribution of the NRI component to its analgesic effects. As a consequence, also the occurrence and intensity of opioid-induced side effects should be significantly reduced.

The analgesic properties of tapentadol reside in a single enantiomer and do not require metabolic activation. Accordingly, the relative contributions of the two mechanisms, MOR activation and NRI do not vary during metabolic transformation. MOR agonism allows a reduction in spinal pain transmission as well as actions at supraspinal sites through descending projections that further reduce sensory transmission. The inhibition of NA reuptake enhances the descending inhibition of pain likely via α2 adrenoceptors. Due to a lack of serotonergic activity in tapentadol, pain facilitation via the descending transmission system is not enhanced, and the side effects caused by increased serotonin in the central and the enteric nervous systems (constipation, nausea, vomiting, diarrhoea) are avoided.

Experimentally, tapentadol has been characterised as MOR agonist and NRI, with K_i values of 0.1 μM and 0.5 μM in a rat MOR binding assay and a rat synaptosomal NA reuptake assay, respectively. This represents a MOR affinity 50 times lower than that of morphine. Affinity at the other opioid receptor types (κ-opioid receptor, δ-opioid receptor) and the ORL1 receptor is at least one order of magnitude lower than at the MOR. The inhibition of the serotonin reuptake transporter (K_i = 2.4 μM) is regarded as negligible.

In vivo microdialysis studies in rat ventral hippocampus have shown that tapentadol in the analgesic dose range increases extracellular levels of NA by up to 450% above baseline (Tzschentke et al., 2007). By contrast, morphine at analgesic doses has no consistent effect on hippocampal NA levels. Therefore, this effect of tapentadol is very likely caused through NRI.

In contrast to its moderate MOR binding *in vitro*, *in vivo* testing in rats and mice has shown that intravenous tapentadol has a high potency against acute nociceptive pain, being only 2–3 times less potent than morphine, supporting the idea that the NRI component also contributes to tapentadol's analgesic effects.

By comparing the results obtained in the low-intensity tail-flick test in rats treated with tapentadol combined with the MOR antagonist naloxone or the α2 adrenoceptor antagonist yohimbine, it was possible to establish that MOR agonism has a greater role than NRI in this acute pain model. In different animal models of mono- and polyneuropathic pain, tapentadol also demonstrated high analgesic potency and efficacy (Tzschentke et al., 2007). When in the spinal nerve ligation model tapentadol was combined with antagonists at MOR or α2 adrenoceptors, it was found that NRI now contributed more to its analgesic efficacy than MOR agonism. In contrast, the weak serotonin reuptake inhibition component of tapentadol did not contribute either to its antinociceptive or to its antihypersensitive effect, as the 5-HT2A receptor antagonist ritanserin did not affect the response to tapentadol in either model. These results (see Schröder et al. (2010) for detailed presentation of the respective original data) suggest that tapentadol analgesia in acute nociceptive pain is primarily produced by MOR agonism, while in chronic neuropathic pain the contribution of NRI to analgesia is more pronounced.

The moderate affinity of tapentadol at the MOR and the opioid-sparing effect of tapentadol's NRI component suggest that tapentadol should produce fewer opioid-related side effects than classical MOR agonists, such as morphine. Indeed, when compared to the latter drug, tapentadol produces much less retches and vomits in ferrets, and their duration was shorter. Furthermore, the threshold dose for these effects was 100 times higher for tapentadol than for morphine. In line with these data, tapentadol had a weaker inhibitory effect than morphine at equianalgesic intraperitoneal doses on both (i) gastrointestinal motility assessed from charcoal transit and (ii) prostaglandin-induced diarrhoea (Tzschentke et al., 2006).

The endogenous opioid as well as the monoaminergic systems play key roles in the processing of nociceptive and neuropathic pain. While opioids and NA have clearly inhibitory functions, 5-HT can either inhibit or facilitate pain nociception.

Therefore, the pharmacological profile of tapentadol – combining MOR agonism and NRI in the same single molecule – appears to be equally well suitable for the treatment of many different types of pain and differentiates it from other centrally-acting analgesics. Tapentadol possesses both antinociceptive and antihyperalgesic/antiallodynic properties, and is associated with a better side effect profile than classical opioids, due to its opioid-sparing effect and the absence of serotonergic activity. The Phase III clinical trials carried out so far in patients with moderate to severe acute and chronic pain conditions corroborate the preclinical findings, demonstrating that tapentadol has broad efficacy for many different types of pain and superior tolerability to classical opioids (see Hartrick, 2009, for review of clinical trials in acute pain).

In view of the unique pharmacology of tapentadol, as outlined by Schröder et al. (2010), and in line with the opinion of the above mentioned panel of expert pharmacologists, it seems reasonable to propose that with the new analgesic drug tapentadol a new class of centrally-acting analgesics, designated MOR-NRI, has appeared on stage.

Acknowledgements

The round-table conference on the role of opioid and monoaminergic systems in pain processing, and on the pharmacological profile of tapentadol took place in Madrid on June 20–21, 2009, and was attended by F. Porreca, USA, A.H. Dickenson, United Kingdom, P.L. Canonico, Italy, A. Dahan, The Netherlands, A.C. Falcão, Portugal, M. Hamon, France, E. Högestätt, Sweden, J.A. Micó, Spain, B.E. Przewlocka, Poland, M. Schäfer, Germany, and H.U. Zeilhofer, Switzerland.

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Available online 24 July 2010