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REVIEW

Pharmacological rationale for tapentadol therapy: a review of new evidence

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Abstract: Chronic pain could be considered as a neurological disorder. Therefore, appropriate selection of the therapy, which should consider the pathophysiological mechanisms of pain, can result in a successful analgesic outcome. Tapentadol is an analgesic drug which acts both as a μ-opioid receptor (MOR) agonist and as a noradrenaline reuptake inhibitor (NRI), thereby generating a synergistic action in terms of analgesic efficacy, but not for the burden of adverse effects. Therefore, tapentadol can be defined as the first "MOR-NRI" drug. This molecule holds the potential to address at least some of the current limitations of analgesic therapy due to its unique mechanism of action and has shown to be safe and effective in the treatment of chronic pain of cancer and noncancer etiologies including nociceptive, neuropathic and mixed pain. In particular, the MOR component of tapentadol activity predominantly allows for analgesia in nociceptive pain; on the other hand, the NRI component contributes, now in a predominant manner, for analgesic efficacy in cases of neuropathic pain states. This paper will discuss recent pieces of evidence on the pathophysiology of pain, the background on tapentadol and then present some new studies on how the unique mechanism of action of tapentadol provides a key role in its analgesic efficacy in a number of pain states and with a favorable safety profile.
Keywords: tapentadol, neuropathic pain, pain chronicization

Introduction

Chronic pain results from a maladaptive functional and structural transformation of neural circuits occurring over time at peripheral and central sites in the neural pathways from peripheral nerves to higher centers.[1] Therefore, if the selection of the therapy takes into account the pathophysiological mechanisms of pain, a successful analgesic outcome is more likely.

It is widely accepted that the neurobiological modifications occurring in chronic pain can be major contributors to the poor efficacy shown by analgesic therapy.[2,3] Moreover, available analgesic options are not always applied in accordance with the growing understanding of the mechanisms underlying both acute pain and the transition processes leading to chronic pain.[1] It is generally accepted that pain can be divided into nociceptive (generally pain arising from inflammatory processes due to tissue damage), neuropathic (arising from a lesion or disease of the somatosensory nervous system), and mixed pains such as low back pain and cancer pains where both types of pain can co-exist. Importantly, analgesics acting at the periphery have to be targeted to the type of pain – NSAIDs for nociceptive pains or ion channel modulators for neuropathic pain, whereas centrally acting drugs may have much broader indications.[4]

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Tapentadol acts both as a μ-opioid receptor (MOR) agonist and as a noradrenaline (NA) reuptake inhibitor (NRI), thereby generating synergistic analgesic action.[5–7] The elevated NA at spinal synapses leads to inhibition of pain signaling through activation of the inhibitory post-synaptic α-2 adrenoceptor on spinal nociceptive neurones, an action that mimics activity in certain descending inhibitory pathways from brain to spinal cord. Tapentadol, therefore, can be defined as a "MOR-NRI" drug. This molecule holds the potential to address at least some of the current limitations of analgesic therapy in terms of mechanism of action and has shown to be safe and effective in the treatment of several types of chronic pain, including nociceptive, neuropathic, mixed and cancer pains.[8,9]

Here we discuss, in the light of mechanisms contributing to the pathophysiology of pain, how the novel mechanism of action of tapentadol forms a basis for analgesic efficacy in nociceptive, neuropathic and mixed pains with a reduced side-effect profile compared with classical MOR agonists.

Pathophysiology of pain: new evidence

The importance of central sensitization

According to standard classifications, pain can be distinguished into nociceptive pain (originating in tissues in response to nociceptor stimulation) and neuropathic pain, which originates in the peripheral or central nervous system following a lesion or disease to sensory nerve fibers.[1] In both cases, nociceptive impulses propagate along thinly myelinated A-delta and unmyelinated C-fibers, first-order peripheral nociceptive neurons and are then transmitted to second-order neurons in the spinal cord dorsal horn (Figure 1). In turn, these neurons that integrate and modulate the incoming sensory information, transmit ascending pain messages via the thalamus to cortical sensory areas where both the intensity and location of pain are determined. Pathways from the spinal cord to the limbic brain lead to the aversive and threatening nature of the stimulus. Activity in these higher centers allows for the patient to build up their personal pain experience.

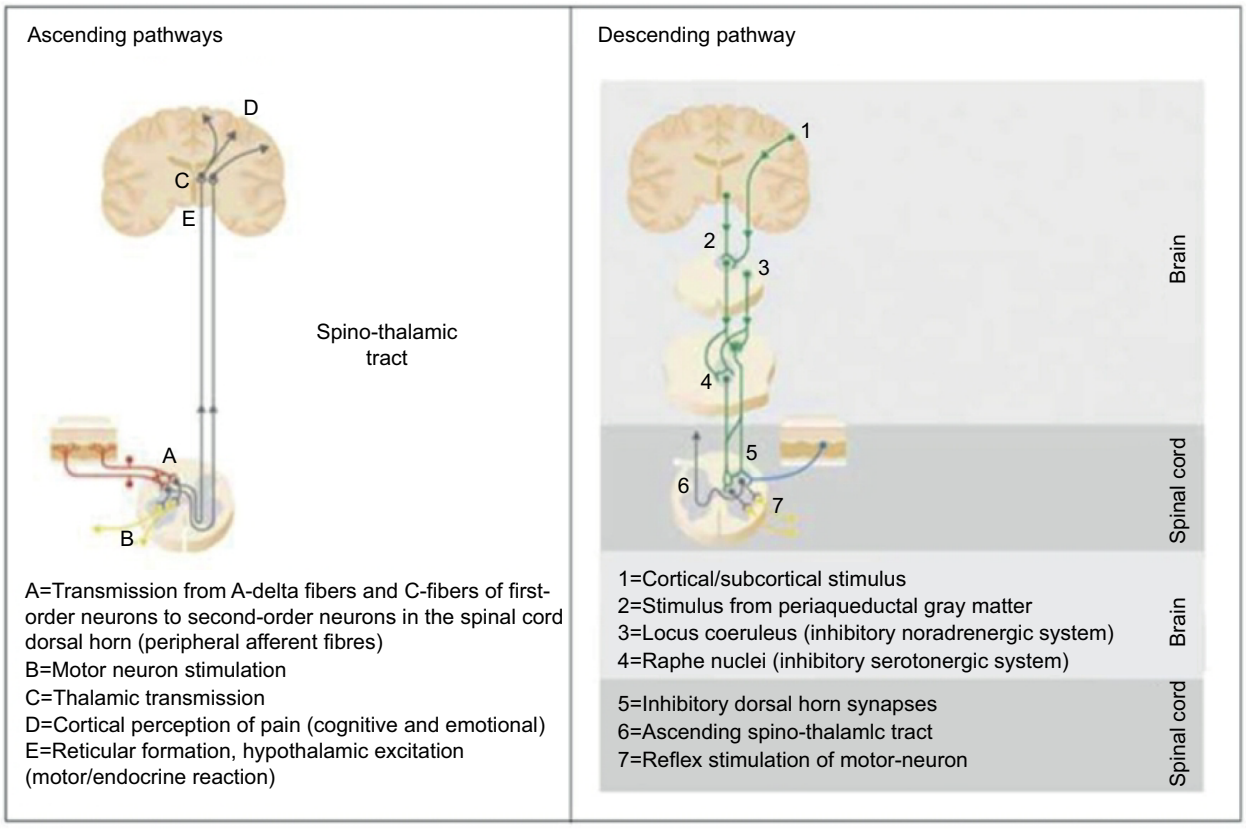

Figure 1 Ascending and descending pathways involved in pain transmission and modulation.
Note: Reproduced with permission from Coluzzi F, Fornasari D, Pergolizzi J, Romualdi P. From acute to chronic pain: tapentadol in the progressive stages of this disease entity. *Eur Rev Med Pharmacol Sci.* 2017; 21(7):1672–1683.[1]

The transmission of noxious stimuli along the ascending pathways is influenced by the action of descending modulatory pathways. These pathways, especially at the spinal cord level, may modify the intensity and characteristics of the perceived pain. In particular, at spinal synapses, the descending pathways promote the release of several mediators, including endogenous opioids, NA, serotonin (5-HT) and γ-aminobutyric acid (GABA), which modulate the transmission between primary and secondary neurons.[1]

As recently reviewed, over the last few years mounting attention has been paid to the processes that lead to chronic pain, which encompasses a number of functional and structural modifications of the involved structures.[10] Indeed, from the very early stage of acute pain (few hours), the neural structures involved in pain start to undergo plastic modifications so that peripheral and central sensitization can ensue. Tissue damage or nociceptor activation can lead to peripheral sensitization: peripheral nociceptors reduce their activation threshold and increase their responsivity to noxious stimuli. If the cause of the inflammatory pain resolves within a few days, such plastic modifications also regress.[1,10] In cases of neuropathic pain, abnormal impulses in damaged and undamaged nerves as a result of altered ion channel activity and expression are sent to the spinal cord.[1] In both cases, if the stimulus persists, high-frequency transmission is upheld with massive spinal release of glutamates and neuro-modulating peptides. This release of neurotransmitters ultimately leads to modifications of the spino-thalamic neurons and interneurons, promoting increased excitability, a phenomenon known as central sensitization. Central sensitization may also involve other supraspinal integration structures, such as the thalamus and cortex, further promoting the transition to chronic pain.[11] These modifications are mainly of functional nature (eg, enhanced activity of single neurons, recruitment of silent synapses and synaptic reinforcement) and are reversible in most cases.[12] In this context, persistence of the peripheral nociceptive input and the reduction in the efficacy of some spinal inhibitory systems (eg, the GABAergic system) may also participate in the changes that lead to pain becoming chronic. In many studies on nociceptive and neuropathic pain models, the failure of descending inhibitory systems from the brain to spinal cord represents a key contributor to the enhanced pain condition.[13]

Importantly, understanding peripheral and central sensitization and the changes in descending systems may promote improved diagnosis and tailoring of treatment in patients with chronic pain, as well as the development of new regimens for mechanism-based therapy. Some of the mechanisms underlying these changes in pain processing can be translated from animals to humans providing new options in design of therapies and profiling drugs under development.

Pain evolution

According to available evidence, the process of chronification of pain could be divided into three consecutive stages.[1,14] The first stage, acute pain, is characterized by localized pain, with intensity proportional to the stimulus or tissue damage. The pain usually resolves rapidly and often with anti-inflammatory drugs; lack of modulation of such episodes must not be underestimated, since they may ultimately trigger the more progressive stages. Noteworthy, neuropathic pain may take longer to become established as a lesion or disease causing the damage and dysfunction of the affected nerves develops. Neuropathy leads to numbness as nerves become disconnected from their peripheral targets but a significant number of patients have pain that may be ongoing or evoked, superficial or deep and described using particular sensations such as shooting, burning, electric-shock like, all indicative of abnormal nervous conduction.

In the second stage, defined as "progressive recurrent pain", the pain has not yet become chronic. However, more frequent and intense episodes of pain may occur, with the interval between them being either entirely pain-free or characterized by mild persistent pain; central sensitization and altered descending control phenomena start developing leading to expanded areas of pain and more hyperalgesia and allodynia, and possibly even structural modifications may occur if pain is not adequately treated. This type of pain is likely responsive to effective treatment, and therefore the early establishment of appropriate therapy is of paramount importance.

In the third and final stage, the changes in the processes of pain have become established in the periphery, spinal cord and higher centers and both transmission and modulation pathways now may present pathological properties with a gain of excitation and a loss of inhibition. With increasing complexity, the pain becomes more difficult to control and stabilize. In clinical practice, it is paramount to attempt to recognize each stage and establish appropriate treatment as early as possible with the aim to prevent the progression of pain to a chronic state. In this phase, central sensitization and other changes becomes more and more established, contributing to a number of different pain conditions (Table 1). Moreover, as pain becomes chronic, quality of life reduces,

Table 1 Chronic pain conditions in which different aspects of the central sensitization phenomenon have been assessed and validated mechanistically with quantitative sensory testing

Chronic fatigue syndrome
Chronic low back pain
Chronic pancreatitis
Endometriosis
Fibromyalgia
Irritable bowel syndrome
Migraine
Multiple chemical sensitivity
Myofascial pain syndrome
Neurogenic pain
Non-cardiac chest pain
Osteoarthrosis
Pelvic pain/interstitial cystitis
Post-traumatic stress disorder
Postoperative chronic pain
Primary endometriosis/dysmenorrhea
Restless legs
Rheumatoid arthritis
Shoulder impingement syndrome
Temporomandibular disorders
Tension type headache/chronic tension type headache
Vulvodynia
Whiplash

Note: Data from Arendt-Nielsen et al.[10]

and the patients may experience mood alterations, depression and/or anxiety, and diminished ability to carry out daily activities.[1,10]

Crucial role of descending pathways

Descending facilitatory and inhibitory pathways originating in supraspinal centers could influence the perception of pain and modulate the activity of spinal nociceptors through increased or decreased propagation of signals to the brain.[13,15] The release of neurotransmitters, including endogenous opioids, NA and 5-HT, underlies the modulation of the noxious stimulus.

MOR agonists inhibit transmission of pain signals along the ascending pathways and are involved in the modulation of supraspinal pain signals through their action in descending pathways.[1,16] Noradrenergic pathways exert an inhibitory effect on the transmission of acute pain, and changes in these systems appear to contribute to chronic pain.[17] Conversely, serotoninergic pathways may have a facilitatory effect particularly in the advanced stages of chronicity and are, therefore, pro-nociceptive.[13,18] An imbalance between amplified spinal ascending signals and inadequate activation of the descending inhibitory pathways has been suggested to lead to the development and maintenance of many chronic pain syndromes.[13]

Experimental evidence suggests that effective involvement of inhibitory descending pathways could protect against the development of chronic pain.[19] Moreover, the MOR activation is particularly relevant in acute nociceptive pain, while the inhibition of NA reuptake activity plays a crucial role in chronic neuropathic pain.[20]

A number of analgesic drugs can either interact with or have their actions modulated by these systems, reinforcing their importance in the establishment of pain, but also in its control. However, until recently, a molecule endowed with the ability to restore physiological balance between ascending and descending pathways was not available in clinical practice.[21]

Pharmacology of tapentadol

Mechanism of action

Tapentadol is a novel, centrally acting analgesic drug. It is the first representative of a new class of drugs, which can be referred to as MOR-NRI drugs, and it displays an analgesic efficacy comparable or superior to that of strong classical opioids such as oxycodone and morphine.[5,6,22,23] Noteworthy, this molecule was synthetized by a rational drug-design program aimed at defining a molecule characterized by both MOR and NRI activity.[6,21] Despite a 50-fold lower affinity for MOR and relatively moderate NRI activity (Ki =0.48 μM for rat synaptosomal uptake inhibition) tapentadol potency is comparable to that of morphine across a variety of preclinical pain models.[24] As previously documented,[25] such potency cannot be explained by a simple additive effect, but rather by a synergistic interaction between the two distinct mechanisms of action within the single molecule. Thanks to this intricate interaction and mutual enhancement of the individual effects, relatively moderate receptor activities are sufficient for both mechanisms of action to achieve a strong analgesic effect by acting on both ascending and descending pathways (Figure 2). Importantly, the two mechanisms do not interact synergistically on the burden of adverse effects.[6,26] Remarkably, a very recent study suggested that the "μ-load" of tapentadol is ≤40%, relative to pure MOR agonists, which have, by definition a μ-load of 100%.[27] This reduced μ-load likely translates into a more favorable tolerability profile of tapentadol compared with strong classical opioids. Moreover, tapentadol shows minimal serotoninergic activity.[28] This pharmacological profile may have importance in chronic therapy, since the activation of serotoninergic pathways produce pro-algesic effects and may also stimulate emesis

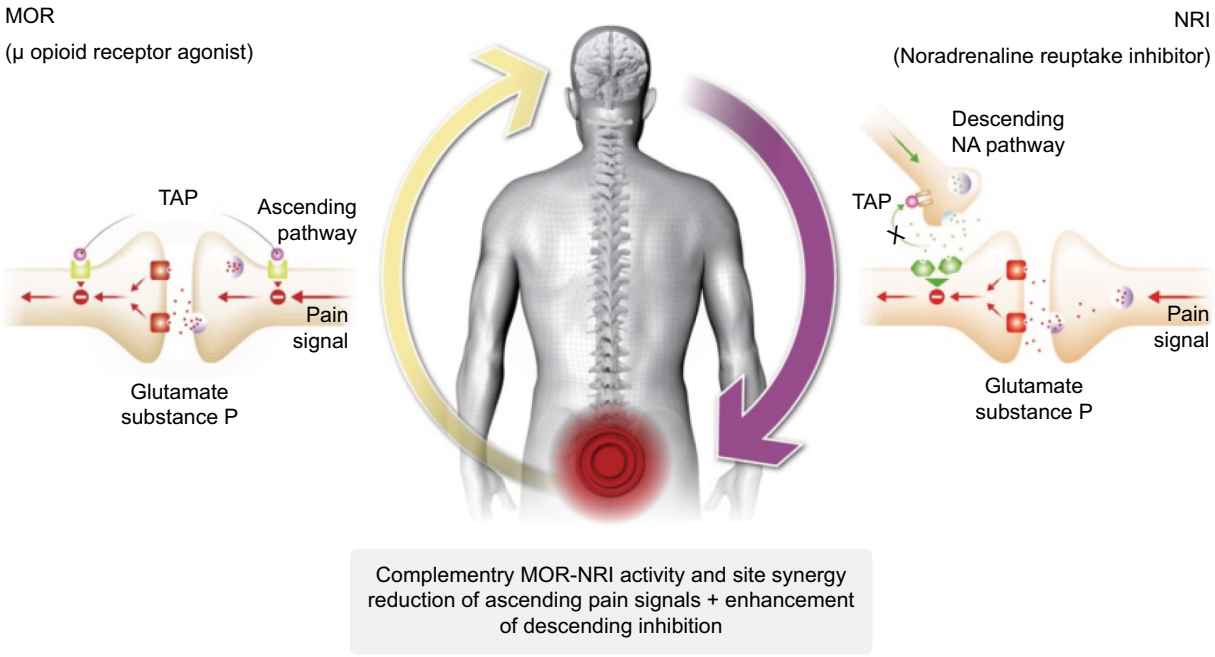

Figure 2 Tapentadol: mechanism of action at spinal level.
Abbreviations: MOR, μ-opioid receptor; NRI, noradrenaline reuptake inhibitor; NA, noradrenaline; TAP, tapentadol.

over time.[13,18] The potential synergic effect of tapentadol has also been preliminarily assessed.[29,30]

Experimental evidence

Some previous experimental evidence is worth consideration. Tapentadol has been demonstrated to partially retain its analgesic efficacy in knockout mice with a genetic deletion of MOR,[31] thus confirming the relevance of its noradrenergic component for pain relief. Using in vivo electrophysiological tests in spinal nerve ligated and sham-operated rats, systemic tapentadol dose-dependently reduced evoked responses of spinal dorsal horn neurons to a range of peripheral stimuli.[32] Moreover, spinal application of opioid receptor or selective α-2-adrenoceptor antagonists produced near complete reversal of the inhibitory effects of tapentadol, thus suggesting that no mechanisms other than MOR-NRI is involved in tapentadol-induced analgesia. In another animal study, the effects of systemic morphine, tapentadol or duloxetine were evaluated in rats with spinal nerve ligation (SNL) or sham surgery.[33] Response thresholds to von Frey filament stimulation decreased significantly from baseline in SNL, and not in sham rats. All molecules produced reversal of tactile hypersensitivity. In more detail, duloxetine increased spinal CSF NA levels in both sham and SNL rats, but no significant differences were observed in animal groups. Tapentadol induced a significant increase in spinal NA levels in SNL, but not in sham, rats. At a higher dose, tapentadol increased spinal CSF NA levels in both SNL and sham groups; however, spinal NA levels were elevated for an extended period in SNL rats. This could be detected rapidly following tapentadol in both sham and SNL groups. On the other hand, morphine reversed tactile hypersensitivity in nerve-injured rats, but CSF NA levels were significantly reduced after MOR agonist administration in both sham and SNL rats. Overall, these data suggest that, in a model of experimental neuropathic pain, tapentadol and not morphine, induces enhanced spinal NA levels, thus offering a mechanistic correlate to observed clinical efficacy and side-effect profiles in this pain state and a clear differentiation between a pure MOR and MOR-NRI. Indeed, NA is a key transmitter in descending inhibitory controls and in many pain conditions, the balance between central inhibitory NA and excitatory 5HT actions shifts leading to a gain of pain facilitation.[13]

In another study in a rat model, the acute effects of tapentadol in the locus coeruleus (LC), a central nucleus, which is critical in pain modulation and is regulated by the noradrenergic and opioid systems were investigated.[34] Overall, tapentadol inhibited the spontaneous electrophysiological activity of LC neurons in a dose-dependent manner. This inhibitory effect was reversed by both α-2-adrenoceptor antagonists and MOR antagonists. Furthermore, tapentadol inhibited LC response to mechanical stimulation in a dose-dependent manner. Thus,

acute administration of tapentadol inhibits LC neurons in vivo, mainly due to the activation of α-2-adrenoceptors; moreover, these data further confirm that both the noradrenergic and opioid systems participate in the inhibitory effect of tapentadol on LC neurons, accounting once again for the potent analgesic effect of tapentadol and its mild opioidergic side effects.

In a model of cancer pain, tapentadol administration resulted in marked inhibitions of the neuronal activity with efficacy against mechanical, thermal and electrically evoked activity.[35] The effects of tapentadol were fully reversible by the MOR antagonist naloxone and partly by the α-2-adrenoceptor antagonist atipamezole, again supporting the idea of MOR-NRI synergistic actions.

Last, tapentadol seems to be protective of splenic cytokines differing from morphine, which exerts a generalized suppression on all cytokines.[36]

Human studies

Niesters et al[38] investigated the influence of tapentadol on conditioned pain modulation (CPM; the human counterpart of diffuse noxious inhibitory controls), a descending inhibitory system that uses NA and subsequent activation of the α-2-adrenoceptor[37] and offset analgesia (OA, a test in which a large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation).[38] In total, 24 patients with diabetic polyneuropathy (DPN) were randomly assigned to either tapentadol prolonged release (PR) or placebo for 4 weeks. Before treatment, no patient showed CPM or OA responses. At 4 weeks, CPM was significantly activated by tapentadol PR compared with placebo (24.2 vs 14.3%; $P<0.001$); relief of DPN pain was also greater in patients on tapentadol compared with placebo ($P=0.028$). On these bases, the authors of the study concluded that the analgesic effect of tapentadol in patients with DPN is dependent on the activation of descending inhibitory pain pathways. This back translates perfectly to the preclinical data that also shows a restoration of diffuse noxious inhibitory controls in neuropathic models by the drug. Most importantly, this preclinical study revealed that diffuse noxious inhibitory control was an NA-mediated descending inhibition that is lost in a model of neuropathic pain. Thus, the ability of tapentadol to restore CPM is a perfect translation from the preclinical to clinical domain and moreover, such clinical data are in line with the NRI-mediated analgesic component of the drug.[37]

Implications for clinical practice

According to the above-mentioned evidence, tapentadol has been described as "one key for two locks," since this molecule presents a chemical structure that can simultaneously interact with both the opioidergic and the noradrenergic systems.[39] This synergistic action represents an important option for the first-line treatment of patients who require both nociceptive and neuropathic pain relief (and therefore also mixed pains), also given its favorable efficacy/side-effect ratio.[40] In particular, the inhibition of NA reuptake is a key mechanism – and may even predominate over opioid actions – in chronic pain states, and especially neuropathic ones, thus reinforcing the notion that tapentadol is markedly different to classical opioids.[21] Moreover, the reduced incidence of some typical opioid-induced side effects, compared with equi-analgesic doses of classical opioids, further differentiate tapentadol from opioids.

Pharmacokinetic properties of tapentadol

Tapentadol follows a linear pharmacokinetics model. Oral adsorption is rapid with Cmax usually reached in less than 2 hours and with a t1/2 of about 4 hours. Since tapentadol is not a prodrug, both its pharmacokinetics and analgesic efficacy are independent of metabolic activation and individual variations among single patients. None of the metabolites of tapentadol have analgesic activity. Moreover, given its metabolism (which is mainly glucuronidation-based), this molecule is associated with a low risk of drug–drug interactions at the cytochrome (CYP) 450 level, and may therefore be used in poly-treated patients.[39] For this reason, tapentadol and its metabolites are almost completely (99%) eliminated in the urine.[41] Therefore, tapentadol should be administered with caution in patients with severely impaired renal function.

In an investigation on the PR formulation, Zannikos et al[42] evaluated the pharmacokinetics of tapentadol administered to healthy subjects enrolled in seven different studies. Overall, maximal tapentadol serum concentrations (Cmax) were observed 5 hours after dosing. Mean terminal half-life ranged from 4.4 to 5.9 hours. Tapentadol Cmax and AUC values increased following single PR doses of 50–250 mg. Tapentadol concentrations increased during repeat dosing and reached the steady-state by the third dose. Coadministration of the 250 mg dose with a high-fat meal increased Cmax and AUC values by less than 17%, thus supporting the use of tapentadol PR without regard to food intake.

Conclusion

The pharmacological profile of tapentadol, combining synergistically MOR agonism and NRI in one molecule, appears to be unique and it seems reasonable to propose for tapentadol

a new class of centrally acting analgesics, designated MOR-NRI.[5] The drug that was developed through a rational drug-design program is characterized by a synergistic MOR-NRI action as shown by multiple biochemical, pharmacological, behavioral and electrophysiological studies in animals. This promotes two forms of inhibition, which allows the restoration of the physiological balance within ascending (MOR action) and descending (NRI action) pathways implied in the pathophysiology of chronic pain. Remarkably tapentadol showed to have only 40% of μ-load compared with a classical opioid at equianalgesic concentration. This reduced μ-load is the result of the combination and synergistic interaction of the two MoAs with regards to analgesia. Due to this, lower opioid activity is needed to reach comparable analgesia and as a result a more favorable tolerability profile is achieved.

Translation of experimental evidence to patients is a crucial issue in pain research. For tapentadol the experimental evidence that NRI is a key mechanism that can be predominant in chronic/neuropathic pain, reinforces the concept that tapentadol is different to classical opioids and may therefore be an a priori choice for the treatment of chronic, neuropathic and mixed pain.[21] This concept has been strengthened and expanded to other drugs (tramadol, buprenorphine, loperamide, cebranopanol) by Raffa et al[27] and Pergolizzi et al.[43] They state that the categorization of all analgesics that have any component of opioid mechanism of action into the same class is anachronistic and misleading; recognition of subclasses of opioids seems warranted scientifically and beneficial to healthcare providers, payers and regulators.[27,43]

Remarkably, through its NRI mechanism, tapentadol restores descending NA inhibitory controls in animals and patients, a rare insight into the mechanistic actions of a drug in humans. In all, tapentadol revitalizes central modulation of pain. The broad effectiveness of tapentadol for nociceptive, neuropathic and mixed pains, due to its combination of MOR agonism and NRI activity, may simplify chronic pain treatment by eliminating the need to isolate and treat the individual types of chronic pain with a combination of different analgesics. Thanks to its low risk of pharmacokinetic interactions, tapentadol may also facilitate chronic pain management in poly-medicated patients, including elderly patients.

Key points

- Tapentadol is the first, and so far, unique agent of a novel class of analgesic agents, and was developed through a rational drug-design program.
- This molecule is characterized by a synergistic MOR-NRI action, allowing the physiological balance to be restored between ascending (MOR action) and descending (NRI action) pathways implied in the pathophysiology of chronic pain.
- Remarkably, the MOR component accounts only for 40% of the total: this reduced μ-load is the result of the combination and synergistic interaction of the two MoAs with regards to analgesia and may result in a more favorable tolerability profile.
- This peculiar mechanism of action suggests that tapentadol may be useful in patients with nociceptive, neuropathic and mixed pain.

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