

Review

Focus on pain mechanisms and pharmacotherapy in the treatment of fibromyalgia syndrome

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Received on December 11, 2008; accepted in revised form on April 28, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 56): S86-S91.

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Key words: Fibromyalgia, pain pathways, pharmacotherapy, muscle, fatigue.

ABSTRACT

Objective. To critically evaluate the role of several notable 'pain pathways' in the fibromyalgia syndrome (FMS).

Methods. PubMed provided the data base for peer-reviewed basic and clinical science studies on musculoskeletal and neuropathic pain mechanisms with a principal emphasis on critically appraising papers from 2002 to the present.

Results. FMS pharmacotherapy is more prevalent in clinical practice as our understanding of the cellular, molecular and pathophysiologic mechanisms contributing to widespread musculoskeletal and neuropathic pain has emerged. Thus, several 'pain pathways' including high-voltage activated Ca^{2+} channels and the K_v1 family of K^+ channels ion channels appear related to the efficacy of pregabalin and amitriptyline, respectively, in FMS. Additionally, serotonergic and serotonergic/norepinephrine receptor-mediated mechanisms may explain the reported pharmacologic efficacy in FMS of mirtazapine, duloxetine and milnacipran. By contrast, the decreased level of μ -opioid receptors in the CNS of FMS patients suggests a mechanism as to why opioid therapy should be avoided. However, increased peripheral benzodiazepine receptors on monocytes from FMS patients suggested an explanation for the reported efficacy of olanzapine in FMS.

Conclusion. Pregabalin was the first drug approved by the FDA for the treatment of FMS-related pain. Drugs that have been assessed for their potential use in FMS pharmacotherapy include gabapentin and tricyclic antidepressants. These drugs appear to target specific Ca^{2+} or K^+ ion channels notable for their involvement in mediating neuropathic pain. Serotonin and norepinephrine reuptake inhibitors including, mirtazapine, duloxetine and

milnacipran appear to be more efficacious in FMS than selective serotonin reuptake inhibitors. Milnacipran became the second FDA-approved drug for FMS.

Introduction

Fibromyalgia syndrome (FMS) is a chronic musculoskeletal condition engendered by eliciting effusive pain via specific physical manipulation in at least 11 tender points among a specific group of 18 anatomically defined structures (1-6). FMS primarily affects middle-aged women. In order to make a diagnosis of FMS this type of pain should be of a persistent nature for 3 continuous months or more (1).

In agreement with the view recently proposed by Henricksson (7), FMS should now be redefined as a multisystemic disease rather than a syndrome. Thus, generalised mechanical pain hypersensitivity also termed allodynia (8), is not limited to tender points and hyperalgesia. Additionally, functional dysautonomia appears to distinguish the pain mechanisms inherent in FMS from other types of musculoskeletal pain. Moreover, several co-morbidities often accompany the musculoskeletal pain component of FMS. Thus, organ systems that are affected in FMS can be widespread such that the physical symptoms in FMS often also include paresthesias, headache, irritable bowel syndrome, chronic fatigue (1) also known as 'fibrofog', diffuse myalgias and generalised anxiety (9), depression, panic and post-traumatic stress disorder (10) as well as disturbances in sleep quality (11-13) and sexual functioning (14).

Although a variety of non-pharmacologic interventions have been employed to improve the quality of life of patients with FMS including patient education, cognitive behavioural therapy, exercise and physical therapy

Competing interests: none declared.

(8, 15, 16), the management of FMS using pharmacotherapy has improved. Thus, despite the fact that a discrete cause for FMS has yet to be identified (17), there has been a recent leap in our understanding of the underlying cellular, molecular and pathophysiologic mechanisms in FMS that contribute to its neuropathic pain component. These include dopaminergic, opioidergic, and serotonergic abnormalities (18), hypothalamic-pituitary-adrenal (HPA) axis dysfunction (19-22) as well as defective nociceptive input (23, 24). Defects in nociception have also been associated with activation of glia which leads to elevated levels of pro-inflammatory cytokines, including tumour necrosis factor- α , interleukin-6 (IL-6), IL-1, as well as substance P, nitric oxide, prostaglandins, excitatory amino acids, ATP and fractaline (25). In that regard, the elevated level of substance P in cerebrospinal fluid has been cited as contributing to a mechanism explaining defective nociception (25). Thus, in this setting Staud (25) has proposed that after central sensitisation occurs only minimal nociceptive input is required to maintain chronic pain. Of note, this latter pathway also appears to involve dorsal horn mechanisms, namely, N-methyl-D-aspartate (NMDA) and neurokinin-1 receptors (26) (see below). Furthermore, by focusing on exploiting the physiologic responses in FMS as a function of the biologic activity of these

various 'pain pathways' a more significant orphan use of specific pharmacotherapy for treating the pain of FMS has emerged. The continuing investigation into new 'pain pathways' may provide the direction needed for developing novel agents for the pharmacotherapy of FMS.

What are the pain mechanism pathways that are relevant to FMS?

Activated Ca^{2+} channels

An increased search for alternative high-voltage activated Ca^{2+} -channel antagonists is likely to emerge following the FDA approval of pregabalin, a synthetic molecule (*i.e.* S (+)-3-isobutyl γ -aminobutyric acid) that is structurally related to γ -aminobutyric acid (GABA) for the treatment of patients with FMS (27, 28). In an 8-week trial, pregabalin monotherapy was effective in improving several of the core clinical symptoms of FMS, including pain, fatigue and sleep disturbance as well as having a palliative effect on the quality of life (27). The side effects attributed to pregabalin monotherapy for FMS were mainly dizziness, somnolence (27, 28) and a higher incidence of peripheral edema compared to placebo (27). Neuronal voltage-dependent Ca^{2+} -channels contain pore-forming α_1 subunits and two ancillary subunits termed, β and $\alpha_2\text{-}\delta$. Four mammalian β subunits (as a result of differential splicing) and 3 $\alpha_2\delta$ units were found in brain (29, 30) and older studies had suggested that the

α_1 subunit was the putative binding site for Ca^{2+} channel antagonists (30).

From a functional perspective, dihydropyridine (DHP)-sensitive L-type Ca^{2+} channels (*i.e.* ion channels that are sensitive to drugs such as verapamil) have been shown to mediate the voltage-dependent Ca^{2+} influx within subcellular compartments. Thus, L-type Ca^{2+} channels regulate the release of neurotransmitters, dendritic action potentials, excitation-contraction as well as molecular coupling events that link excitation to gene transcription (31, 32).

More recent studies have shown that the Ca^{2+} channel $\alpha_2\text{-}\delta_1$ subunit is more likely to be the actual binding site for pregabalin (33). In that regard, the binding of pregabalin (25 nM-2.5 μ M) to cultured neonatal rat dorsal root ganglion neurons reduced their excitatory properties in a concentration-dependent manner which also correlated with a 20%-30% reduction in the high-voltage activated Ca^{2+} current produced by these cells (34). Interestingly, in the same study gabapentin, another agent with demonstrated efficacy for the management of pain in FMS (see below) failed to have any additive effects to that produced by pregabalin indicating that both pregabalin and gabapentin acted on the same-type(s) of L-type voltage-activated Ca^{2+} channels. However, the majority of these Ca^{2+} channels failed to respond to either drug.

In a recent review summarising the results from several studies, Gajraj (35) concluded that pregabalin avidly bound to the $\alpha_2\text{-}\delta$ subunit where it altered Ca^{2+} influx at nerve terminals. Through this mechanism, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, serotonin, dopamine, and substance P. However, in contrast to verapamil, pregabalin was shown to have no effect on arterial blood pressure or on cardiac function.

The complex nature of Ca^{2+} channel responses to gabapentin and pregabalin must, however, also be taken into account. Thus, Bertrand *et al.* (36) showed that gabapentin could also act through G-protein coupled GABA_B receptors to selectively inhibit N-type (*i.e.* DHP-resistant, ω -conotoxin-sensitive) Ca^{2+}

Table I. A relationship exists between pain pathways and the pharmacotherapy of FMS.

Pain pathway	Drug tested	Reference
Activated Ca^{2+} channels	Pregabalin	34
	Gabapentin	36, 37
	Tri-cyclic Antidepressants	38
K ⁺ channels	Amitriptyline	46-48
NMDA ¹ receptor	MTEP ²	49
Serotonin receptor	Mirtazapine	51
Serotonin reuptake	Paroxetine	54
Serotonin/Norepinephrine reuptake	Duloxetine	56
	Milnacipran	57, 58
PBR ³	Olanzapine	66
GHB ⁴	Sodium oxybate	69

¹ N-methyl-D-aspartate; ² 3-[(2-methyl-1, 3 thiazol-4-yl) ethynyl-pyridine]; ³ Peripheral benzodiazepine receptors; ⁴ Gamma-hydroxybutyrate.

channels in hippocampal pyramidal neurons. By contrast, pregabalin binds to neither GABA_A nor GABA_B receptors, nor does it alter GABA uptake or degradation (37).

Finally, the L-type Ca²⁺ channel blocking effects of tricyclic antidepressants (38) which have also shown efficacy in FMS (39-44) must also be considered an additional potential pathway whereby the neuropathic pain of FMS is attenuated by these drugs.

K⁺ channel modulation

The delayed rectifier K⁺ channels belonging to the K_v1 family, and in particular, K_v1.1 and K_v7.2/K_v7.3, have been implicated in neuronal excitability (45). In a recent study (46), amitriptyline was shown to inhibit K_v1.1 and K_v7.2/K_v7.3 channels in a dose-dependent and toxicologically relevant manner in human embryonic kidney 293 cells and in Chinese hamster ovary cells. The inhibitory effect of the tricyclic antidepressant drug, amitriptyline on K_v1.1 and K_v7.2/K_v7.3 channels was reversed by N-[2-amino-4-(4-fluorobenzylamino)phenyl] carbamic acid ethyl ester, a novel anticonvulsant (47), which was previously shown to activate neuronal KCNQ-type K⁺ channels by inducing a large hyperpolarizing shift of steady-state activation. These *in vitro* results support the view that K_v1.1 and K_v7.2/K_v7.3 channels play a significant role in regulating the excitatory nociceptive pathway common to pain-sensing neurons. Furthermore, these K⁺ channels appear to be the likely molecular mechanism that is affected *in vivo* by amitriptyline. Thus, K⁺ channel blockers prevent amitriptyline analgesia and N-(2-amino-4-(4-fluorobenzylamino)phenyl) carbamic acid ethyl ester (retigabine) reduced neuropathic pain even in the presence of amitriptyline. Additionally, these findings offer considerable insight into how these drugs could be employed together to control the neuropathic pain of FMS (48).

N-methyl-D-aspartate (NMDA) receptors

Palucha *et al.* (49) presented evidence that blockade of the NMDA subtype

of ionotropic glutamate receptors with 3-(2-methyl-1,3-thiazol-4-yl) ethynylpyridine (MTEP) reduced glutamatergic activity and produced antidepressant effects in Wistar rats. These results suggested that NMDA antagonists might be useful for suppressing nociceptive input as well as being considered efficacious for reducing the clinical signs of depressive illness that is often a co-morbid condition in FMS (10).

Serotonergic circuitry

Agomelatine is a melatonin and serotonin 5-HT_{2c} receptor antagonist which was shown to improve sleep quality by shortening the sleep latency period (50). These findings suggested that a 5-HT_{2c} antagonist might have some efficacy in treating the sleep quality disturbances common to many FMS patients.

In an open-trial 6-week study, the antidepressant drug, mirtazapine, which appears to act as a serotonergic antagonist, produced a ≥40% reduction in pain, fatigue and sleep problems in FMS patients (51). In this small study of 26 FMS subjects, more than 69% of the FMS patients treated with mirtazapine had at least moderate clinical depression prior to administration of mirtazapine and 8 patients presented with mild depressive symptoms during the study period. Moreover, the reduction in pain in the mirtazapine-responsive FMS subjects correlated with amelioration of depressive symptoms as well. In a review of the results from other clinical trial studies (52) it was shown that the FMS co-morbidities of fatigue, irritable bowel and insomnia could also be modulated by serotonin 5-HT₃ antagonists.

Of note, the serotonin 5-HT₃ pathway was shown to be permissive for gabapentin in Sprague-Dawley rats treated by substance-P/saporin ablation (53). The activity of gabapentin in these animals was found to be dependent on neurokinin-1 and the 5-HT₃ receptor. As was previously stated, gabapentin has shown efficacy in modulating the neuropathic pain of FMS (37).

Conversely, a randomised double-blind placebo-controlled clinical trial assessed the effect of controlled-release

paroxetine, a selective serotonin reuptake inhibitor (SSRI), on FMS patients where those subjects showing concurrent mood or anxiety disorder were excluded (54). In this study, a statistically significant effect of paroxetine on the secondary outcome measurements of pain or tender point scores could not be demonstrated. However, the Fibromyalgia Impact Questionnaire (FIQ) total scores showed ≥50% reduction in the paroxetine-treated group compared to placebo (*p*=0.08) suggesting some effect of paroxetine on improving overall well-being.

Serotonin/norepinephrine reuptake inhibition (SNRI)

Serotonin and norepinephrine have long been implicated in modulating the central nervous system descending inhibitory pain pathways (55). In that regard, the effect of duloxetine, an SNRI, on FMS pain was reviewed based on the results of 2 randomised, placebo-controlled double-blind parallel group clinical trials (56). A critical assessment of both clinical trial studies indicated a palliative effect of duloxetine on FMS persistent pain, especially in women. However, Arnold (56) emphasised that safety and tolerability issues may limit the use of duloxetine in FMS. To determine the extent to which the pain of FMS could be alleviated by an SNRI without the side effect profile of drugs such as duloxetine, a nontricyclic compound was studied in a double-blind placebo-controlled clinical trial involving 125 FMS patients. In that study, Vitton *et al.* (57) showed that 75% of milnacipran-treated patients had an overall clinical improvement compared to 38% in the placebo-treated group (*p*<0.01). Furthermore, 37% of the twice-daily milnacipran-treated group reported at least a 50% reduction in pain intensity compared to the placebo group (*p*<0.05) and 84% of all milnacipran-treated subjects escalated to the highest dose (200mg/day) with no tolerability issues or mild to moderate side-effects. The results of this study (57) were confirmed in another 3-month phase II clinical trial in which treatment with milnacipran resulted in a clinical improvement in a pain outcome

measure as well as other constitutional symptoms of FMS, including feeling physically better, a reduction in fatigue and an increase in self-reported overall well-being compared to placebo (58). Of note, the effect of milnacipran in this clinical trial was more pronounced in FMS patients who presented without co-morbid depression. Milnacipran recently received FDA approval for use in FMS.

It is clear that the results from additional phase 3 clinical trial studies will be required in order to fully evaluate the long-term effects of milnacipran for FMS, its optimal dosing regimen and the extent to which milnacipran may interact with other FMS treatment modalities (59). Of note, Professor J. Branco reported at the recently completed EULAR 2008 meeting (60) that in a clinical trial of 884 FMS patients from 83 study centers, milnacipran treatment caused a 30% or more reduction in pain from baseline using the 24-hr recall pain score recorded on an electronic diary Patient Global Impression of Pain rating of either very much improved or much improved. Additionally, there were no differences in the frequency of adverse events between the milnacipran arm and placebo arm in this clinical trial. However, in keeping with recent results reported by Harris *et al.* (61), any assessment of nontrycyclic antidepressant compounds in future FMS clinical trials should also take into account the variability in pain experienced among FMS patients. That study found a large between-subject variation in real-time pain reports which could explain the significant placebo effect seen among FMS subjects in the various FMS clinical trials reported so far.

Additional pain and inflammation mechanisms relevant to FMS

Advanced glycation end (AGE) products, μ -opioid receptor (MOR) and peripheral benzodiazepine receptor availability may also be components of the FMS pain and chronic inflammation circuitry. With regard to AGE products, Ruster *et al.* (62) using immunohistochemistry found increased levels of the AGE product N- ϵ -carboxymethyllysine (CML), the AGE

receptor (RAGE) as well as collagens, CD68-positive macrophages/monocytes and activated nuclear factor- κ B (NF- κ B) in the interstitial connective tissue of muscle from FMS patients. Elevated serum CML levels were also found in FMS patients compared to the control group, but more importantly elevated levels of RAGE were only found in FMS muscle interstitium. The results of this study suggested that accumulation of AGE products such as AGE-modified collagens and RAGE as well as activated NF- κ B in connective tissue from fibromyalgic muscle could contribute to the developing chronicity and spreading of pain as well as a heightened level of inflammatory responses in FMS patients.

In another study, Harris *et al.* (63) examined the extent to which MOR could contribute to the apparent aberrant central neurotransmission often identified as a characteristic of FMS. In a comparison study of 17 FMS patients age- and sex-matched to a group of 17 healthy controls, Harris *et al.* (63) used positron emission tomography to show that the nucleus accumbens, the amygdala, and the dorsal cingulate of FMS patients had reduced MOR expression levels. Moreover, MOR binding potential negatively correlated with affective pain scale measurements in these FMS patients and suggested the distinct possibility that decreased MOR may arise as a consequence of persistent pain that is so common in FMS. The results of this study also offered a mechanism that could account for why exogenous opioids have been anecdotally reported to have reduced or little efficacy in FMS.

Peripheral benzodiazepine receptors (PBRs) availability may also be related to the degree of widespread pain in FMS. Thus, Faggioli *et al.* (64) showed that PBRs were significantly increased ($p < 0.02$) in monocytes derived from patients with active FMS compared to a group of healthy control subjects. This finding suggested yet another receptor-mediated mechanism that could account for the poor regulation of pain and abnormal nociceptive responses in FMS. Furthermore, this documented involvement of the PBR pathway in FMS also

suggested a mechanism for the reported therapeutic effects of benzodiazepines in FMS. Thus, the reported efficacy of the atypical neuroleptic thienobenzodiazepine, olanzapine, as described in a few FMS patient case reports (65) where FMS patients were treatment-resistant to other pain medicines may be related to the PBR mechanism. However, the significant pain reduction associated with olanzapine in FMS patients (based on changes in the pain and interference scales) (66) must be balanced by its reported adverse side effects. These included weight gain, somnolence and sedation which resulted in significant withdrawal from olanzapine treatment.

Finally, γ -Hydroxybutyrate (GHB) is an endogenous short chain fatty acid that is synthesised locally in the CNS and is derived from its parent compound, GABA. GHB appears to act in a neuromodulatory fashion. Sodium oxybate, the sodium salt of GBH is used for oral administration of GBH and in this regard sodium oxybate has most often been employed to prevent cataplexy in patients with narcolepsy and insomnia (67). However, as previously stated, experimental and clinical studies have shown a distinct inter-relationship between disturbances in the sleep-waking brain and widespread musculoskeletal pain and chronic fatigue (11, 12, 13, 68). A recent clinical trial of sodium oxybate (4.5 or 6 gm/night/8 wks versus placebo) was conducted on 188 patients with FMS of which 78% completed the study (69). The primary outcome variable (POV) was a composite score from baseline using the subject's pain rating, FIQ and the Patient Global Impression of Change. The results of this trial showed that the POV and objective sleep quality indices were improved in the sodium oxybate arm at both drug dosages. The improvements in pain rating were correlated with sleep outcomes suggesting that sodium oxybate may provide an additional pharmacotherapeutic option for FMS.

Conclusions

In recent years there have been considerable advances in our understanding

of FMS pain mechanisms at the cellular, molecular and pathophysiologic level. These advances have resulted in a few new pharmacologic interventions showing efficacy in FMS clinical trials as well as in the general and rheumatology practice setting. Thus, pregabalin and milnacipran are the first drugs approved by the FDA which are specifically designed to treat FMS in general medical practice. Additionally, several of the other drugs used in FMS therapy such as gabapentin and some of the tricyclic antidepressants appear to target serotonin, norepinephrine and specific ion channels which may be related to their downstream regulation of neuropathic pain. Of note, the SNRI type of tricyclic anti-depression medicines and nontricyclic drugs exemplified by duloxetine and milnacipran, respectively, appear to be more useful in treating the pain mechanisms in FMS than SSRIs (Table I). However, based on the results of recent studies (63) it has also been proposed that management of FMS with opioid type drugs should be avoided, based in part, on their apparent lack of clinical efficacy as well as the significant reduction in MOR availability in the CNS of FMS patients. Recently, sodium oxybate has also shown clinical efficacy with good tolerability in modulating sleep quality and pain in FMS.

Although it can now be safely concluded that incorporation of pharmacologic management of FMS when combined with non-pharmacologic interventions such as patient education, cognitive and behavioural therapy, exercise and physical therapy has led to an apparent improvement in the quality of life of patients with FMS, it is still too early to conclude that specific pharmacotherapy targeted at musculoskeletal and neuropathic pain mechanism(s) can be employed in these patients over a long-term period of active disease. Additionally, the existence of co-morbid condition(s) commonly found in FMS patients dictates that a firmer understanding of potential drug interactions be pursued if a sustained relief of FMS pain, without adverse side-effects that would lead to drug withdrawal, is to be achieved.

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