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HYPOTHESIS

Ambroxol for the treatment of fibromyalgia: science or fiction?

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Abstract: Fibromyalgia appears to present in subgroups with regard to biological pain induction, with primarily inflammatory, neuropathic/neurodegenerative, sympathetic, oxidative, nitrosative, or muscular factors and/or central sensitization. Recent research has also discussed glial activation or interrupted dopaminergic neurotransmission, as well as increased skin mast cells and mitochondrial dysfunction. Therapy is difficult, and the treatment options used so far mostly just have the potential to address only one of these aspects. As ambroxol addresses all of them in a single substance and furthermore also reduces visceral hypersensitivity, in fibromyalgia existing as irritable bowel syndrome or chronic bladder pain, it should be systematically investigated for this purpose. Encouraged by first clinical observations of two working groups using topical or oral ambroxol for fibromyalgia treatments, the present paper outlines the scientific argument for this approach by looking at each of the aforementioned aspects of this complex disease and summarizes putative modes of action of ambroxol. Nevertheless, at this point the evidence basis for ambroxol is not strong enough for clinical recommendation.

Keywords: Nav 1.8, Nav 1.7, bromhexine, hyperalgesia, sympathetically maintained pain, central sensitization, interleukins, neuropathic pain, sodium channels

Introduction

Fibromyalgia syndrome (FMS) is a chronic, undegenerate symptom complex that is characterized by chronic widespread pain and evoked pain at tender points. Other common symptoms include insomnia, depression, fatigue, stiffness, and gastrointestinal disorders.[1–3] Approximately 2%–5.8% of the population of industrial countries suffer from FMS,[1,4–9] and 80%–90% of patients are female. Although FMS is classified as a noninflammatory disorder, there is increasing evidence for changes in inflammatory mediators,[10–15] and a disturbed balance in pro- and anti-inflammatory cytokines is being discussed.[12,16–18] In addition, it is also considered a stress-related-disorder with dysfunction of the hypothalamic–pituitary–adrenocortical axis.[19–21] Furthermore, increases in oxidative stress and toxic metabolites of lipid peroxidation have been shown for FMS.[22–24] It has been proposed that fibromyalgia could be a sympathetically maintained neuropathic pain syndrome.[25] Moreover, it has been suggested that dorsal root ganglia and peripheral sensory neuron sodium channels may play a major role in fibromyalgia pain transmission.[26]

In previous publications, we described the successful topical treatment of neuropathic pain[27,28] and nociceptive pain[29] with ambroxol cream in a case series. Furthermore, not only have we observed beneficial topical and oral individual treatment results in FMS

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(Figures 1–3; Kern KU. Data on file. Personal clinical observations. 2011–2017) but also other investigators have observed similar effects using oral ambroxol,[30,31] both of which certainly could be regarded as placebo effects at this stage. Ambroxol is a secretolytic substance, but may also potentially influence several pathophysiological mechanisms involved in fibromyalgia. First, ambroxol interferes with oxidative stress and influences cytokines and inflammation.[32,33] Second, ambroxol blocks sodium channels,[34] especially the tetrodotoxin-resistant (TTX-r) channel subtype $Na_v1.8$,[34–36] which is expressed particularly in spinal ganglion cells[37] and in nociceptive, sensory neurons.[37–40] This should limit central sensitization in chronic widespread muscle pain,[41] which clearly also occurs in FMS.[42] Based on these effects, ambroxol may be an interesting treatment approach for FMS, even if detailed examinations concerning these single mechanisms remain to be performed and an influence of ambroxol on inhibitory descending pain pathways, important in FMS, has not yet been examined. The present paper outlines the scientific argument for the treatment of fibromyalgia using ambroxol by looking at many different aspects of this complex disease and summarizes putative modes of action (Tables 1–3, Figure 4).

Skin, mitochondria, and mast cells

Skin condition

Salemi et al[43] detected IL1β, IL6, and TNFα in skin biopsies of a subgroup of approximately 30% of FMS patients, but not in control subjects. This finding was interpreted as the presence of inflammatory foci indicating neurogenic inflammation, which might be the reason for the efficacy of nonsteroidal anti-inflammatory therapy, which has occasionally been reported. IL1β,[44,45] IL6,[44,46,47] and TNFα[44–46,48–52] are inhibited by ambroxol. Blanco et al[53] demonstrated an increased number of mast cells in FMS patients, the secretion of which was also inhibited by ambroxol.[54–56] Other skin biopsies have shown significant mitochondrial dysfunction and an increased level of oxidative metabolites, in conjunction with inflammatory signs[57,58] correlated with pain.[57] Ambroxol also improves mitochondrial dysfunction[59–61] and oxidative stress.[44,60,62–65] Uçeyler et al[66] investigated the gene expression of the proinflammatory cytokines TNFα, IL6, and IL8 and the anti-inflammatory IL10 in skin biopsies of 25 FMS patients, compared these to patients with depression and healthy controls, and found no detectable differences. The results did not support the hypothesis of these cytokines being involved in the sensitization of peripheral nerves in the skin. In one of the most comprehensive investigations with skin biopsies, FMS patients had reduced intraepidermal nerve-fiber density compared to controls, which supports the view that the pain syndrome in a subgroup of FMS patients is partially of neuropathic origin.[67] In vitro and in vivo investigations have demonstrated that ambroxol can relieve neuropathic pain.[28,29,68–71] Our clinical practice observations have shown pain relief in FMS following some oral treatments or topical application of ambroxol 20%

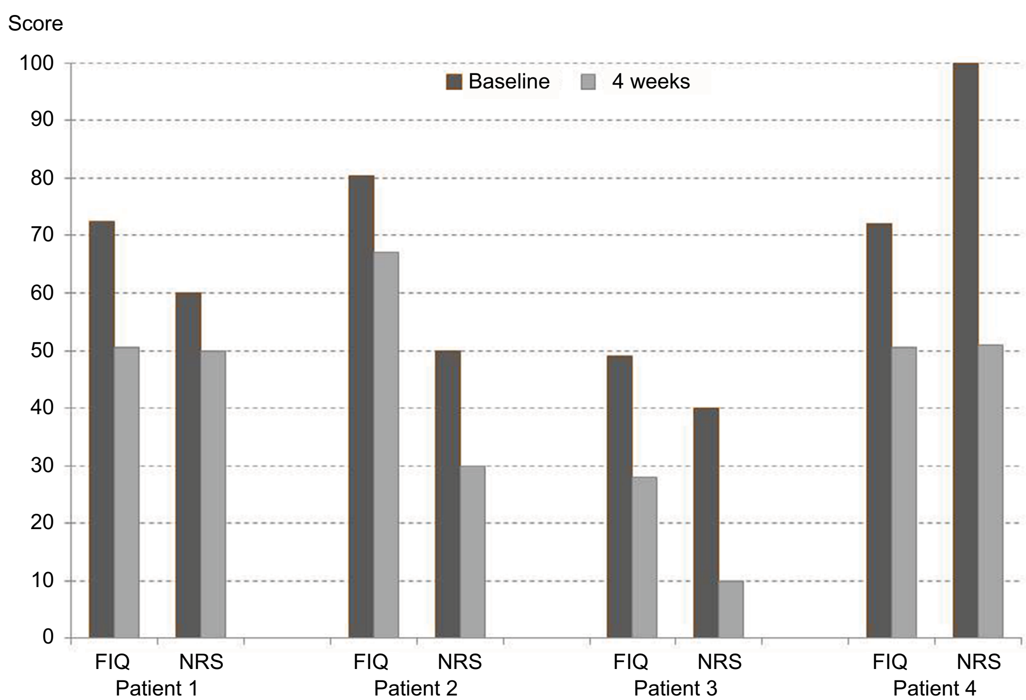

Figure 1 Individual development of FIQ and NRS in four responders to oral ambroxol for fibromyalgia.
Note: 4 weeks of ambroxol orally, 75 mg retarded. Kern KU, data on file - personal clinical observations, 2011–2017.
Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; NRS, numeric rating scale (0–100).

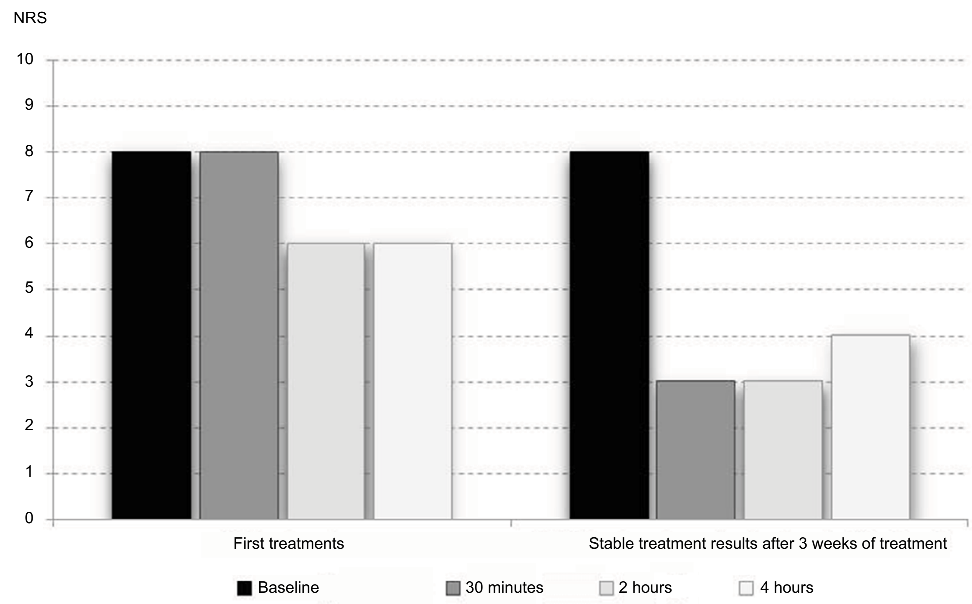

Figure 2 Passage of time of fibromyalgia pain reduction.
Note: Following initial topical ambroxol 20% treatment (hands and elbows) and results after 3 weeks of treatment in a single patient. Kern KU, data on file - personal clinical observations, 2011–2017.
Abbreviation: NRS, numeric rating scale (0–10).

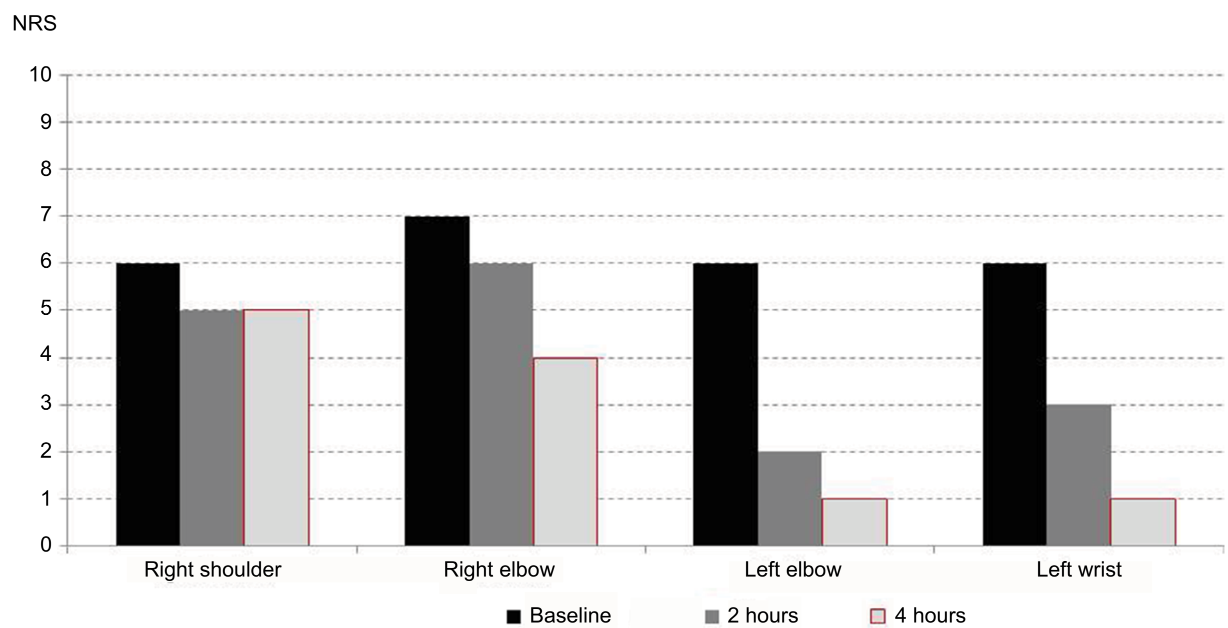

Figure 3 Passage of time of fibromyalgia pain reduction.
Note: Following topical ambroxol 20% treatment of different pain locations (single treatment in a single patient). Kern KU, data on file - personal clinical observations, 2011–2017.
Abbreviation: NRS, numeric rating scale (0–10).

cream (Figures 1–3; Kern KU. Data on file. Personal clinical observations. 2011–2017), which according to the aforementioned relationships need not necessarily be attributed solely to the local anesthetic properties of the compound, especially when improved over time (Figure 2).

Whole-body cryotherapy, beneficial in a subgroup of FMS patients,[72] works primarily via impact on the skin. This therapeutic approach stabilizes lysosomal membranes,[73] among others, and reduces the negative effects of proteins of lysosomal enzymes. Ambroxol has a comparable effect. The compound significantly enhances reduced enzyme activity of the lysosomal glucosylceramidase (in Parkinson's disease),[74–76] as well as α-galactosidase A (in Fabry's disease), α-glucosidase (in Pompe's disease),[77] and β-glucocerebrosidase (in Gaucher's disease).[78,79] At least for the aforementioned diseases, ambroxol is thus clearly an enzyme-modifying therapeutic option.

Table 1 Reported inflammatory and oxidative changes in fibromyalgia, explaining biological pain induction, and potential helpful modes of action of ambroxol

Mechanism	Fibromyalgia	Ambroxol
Inflammation		
Inflammation	Discussed	Anti-inflammatory[32,33,46]
Edema	Common	↓[46,152,326]
Tissue hypoxia and acidosis	Discussed	↓[229]
Cytokines		
Cytokines	Important in FMS[12,13,264] Influence on HPA axis[269–271] Mediator of neuropathic pain[266–268]	Multiple effects on cytokines[32]
Proinflammatory		
IL1β	↑[43,281]	↓[44,45]
IL2	Decreased by therapeutic cryotherapy[73]	↓[49]
IL6	↑[12,14,91,199,200,272]	↓[44,46,47,205]
IL8	↑[12,199,200,273,274,277]	↓[47,96,201–205]
IL8 intrathecally	↑ Compared to rheumatoid arthritis[199]	Reduced allodynia[71]
TNFα	↑[43,91,283,327]	↓[44–46,48–52]
Anti-inflammatory		
IL1RA	↑[12,199]	IL1 ↓[44,45,48,51]
IL4	↓[18,287] ↑ Compared to rheumatoid arthritis[199]	↓[54]
IL10	↑[13,276,278,281,282] Unchanged[12,276]	Stabilization[203,284] ↑[285]
Others		
IL13	↓[287]	↓[54,285] (but helpful as anti-inflammatory)
IL5	↓[287]	↓[54,285] (but helpful as anti-inflammatory)
Cellular immunity	↓[11]	↑[86,87,285] (Na$_v$1.8 immunomodulatory)[295]
NLRP3 inflammasome	Activated[291,292]	↓ (free-radical scavengers)[44,60,62–65]
Mast cells	↑[53,88]	↓[54–56] (secretions)
MCP1	↑[150,274,289] Correlation/pain intensity[150] ↑ in mutation subpopulation[289]	↓[51,95,152]
Oxidative stress		
Oxidative stress	↑[57,84,115]	↓[45,74,96,104,285]
Oxidative metabolites	↑ (multiple, see below)	↓[44,59,62,64,65,96,123]
Lipid peroxidation	↑[23,81]	↓[59,98,99] (inhibition)
Oxidative parameters		
Superoxide	↑[83]	↓[328]
Malondialdehyde	↑[22–24]	↓[59,98,99]
Xanthine oxidase	↑ (and correlation with muscle pain)[100]	↓[45]
Antioxidative parameters		
Catalase	↓[80,81]	↑[62,101]
Glutathione peroxidase	↓[80,81]	↑[45]
Superoxide dismutase	↓[23,24,80]	↑[45,98,101–104]
Antioxidative therapies		
Melatonin	New therapeutic strategy[112,113] Potent antioxidant[114] Lipid peroxidation ↓[110]	Future strategy? Also antioxidant[44,59,62,64,65,96,123] Lipid peroxidation ↓[59,98,99]
Free-radical scavengers	Therapeutic option?[100]	Acts as[44,60,62–65]
Nitrosative stress		
Nitrosative stress	↑[84,115]	↓[96]
Nitric oxide	Correlates with FIQ score[119] Involved in pathophysiology?[97,116] Responsible for pain sensitivity[117] Correlation with pain intensity[118] Nitric oxide synthase inhibitors needed for therapy[120]	↓ (activity and production)[44,121–123]

Abbreviations: FIQ, Fibromyalgia Impact Questionnaire; FMS, fibromyalgia syndrome; HPA, hypothalamic–pituitary–adrenocortical; Na$_v$, voltage-gated sodium.

Reduction of many enzymes is also present in FMS.[23,24,80–82] Low activity of the enzyme prolyl endopeptidase in serum is even supposed to have predictive diagnostic value.[82] The possibility of enhancement of this specific enzyme activity by ambroxol should thus be investigated.

Mitochondria

Mitochondrial dysfunction in FMS has been demonstrated in skin biopsies,[57,58] blood,[83] and muscle cells, and may explain muscular pain.[84] If such mitochondrial dysfunction also occurs in neurons of the central nervous system (CNS),

Table 2 Reported nociceptive and CNS changes, cellular dysfunction, and accompanying symptoms in fibromyalgia

Nociception and CNS	Fibromyalgia	Ambroxol
Muscle pain	Common (multiple)	$Na_v1.8$ in 86% of sensory muscle fibers[329]
	Central sensitization[133–135] and long-lasting TTX-r activation[136]	Blockade of involved $Na_v1.8$ Antioxidative in acidosis[45,74,96,104,285]
	Tissue acidosis crucial[141,142]	Blockade of involved $Na_v1.8$
	ASIC3 essential[139,146] → $Na_v1.8$ activity ↑	MCP1 ↓[51,95,152]
	Induction and sensitization by MCP1[150,151]	Xanthine oxidase ↓[45]
	Correlation with xanthine oxidase[100]	↓ (or improved)[59–61]
	Mitochondrial dysfunction in FMS muscles shown and "explanation"[84]	
Central sensitization	Involved in FMS[42,175,176] and chronic muscle pain[133–136,177]	↓ (via $Na_v1.8$ blockade and reduced inflammation) $Na_v1.8$ blockade helpful or preventive[41,92,178]
	Chronic widespread pain in FMS animal model $Na_v1.8$-associated[41]	
NP	Involved[153–156]	↓[27–29,34,69–71,165,330]
	Cytokines as mediators[266–268]	Multiple effects on cytokines[32]
Allodynia/hyperalgesia	Common[156,180–182]	↓[68,69,71]
Heat hyperalgesia	Reported[156]	Suppressed by 100%[69]
Cold hyperalgesia	Reported[173,185,186]	Reduced by approximately 75%[69]
Mechanical allodynia	Reported[156]	Reduced by approximately 75%[69] Reduced in monoarthritis pain by 50%[69]
Neurodegeneration	↑Peripherally[42,154,162,163]	↓[192,225,229]
	↑ Also in CNS (eye)[162,163]	↓ (improves CNS regeneration)[225]
Small-fiber pathology	Reported[67,159,160,162–164]	Mainly nociceptive C-fibers with expressed $Na_v1.8$[37–40,166–168] and thus blocked NP ↓[27–29,34,69–71,165,330]
SNS	Involved[193–196]	$Na_v1.8$ blockade also on SNS[197,198] IL8 ↓[96,201–205] and so sympathetically maintained pain
Glia	Activation important[17,200,212–214]	Activation ↓: IL8 ↓[96,201–205] and α-synuclein ↓[224]
	Activation increases IL8[207]	
	IL8[206] and α-synuclein increase activation[219]	
Dopamine	↑[221]	α-synuclein ↓[224]
	Dysfunction[221,222]	→ dopaminergic neurodegeneration ↓
	Impaired neurotransmission[223]	
Dysfunction		
Mitochondrial dysfunction	↑ (skin,[57,58] blood,[57,58,83–85] muscle)[84]	↓ or improved[59–61]
	Improvement is therapeutic option[85]	
Lysosomal dysfunction	Whole-body cryotherapy helpful[72,73]	↓[331]
Enzymes	↓[23,24,80–82]	↑ (multiple)[74–79]
	Prolyl endopeptidase reduction predictive[82]	
Cellular immunity	↓[11]	↑[86,87]
IFNγ (immunostimulatory)	↑[332]	↓[49,50,284]
Cortisone receptor	↓[94]	Similar efficacy, but independent[46,51,95,96]
Accompanying symptoms		
Overactive bladder	Common,[296] often painful[298]	Inhibition of overactivity[299]
Irritable bowel syndrome	Common[300,301]	$Na_v1.8$ blockade reduces colon hyperalgesia[307] Dysfunction[234] and visceral pain[308,309]
Dry eyes	↑ in FMS and FMS ↑ in Sjögren's syndrome[311–313]	Increases tear secretion[314] Improves sicca symptoms[315]

(*Continued*)

Table 2 (*Continued*)

Ambroxol treatment		
Ambroxol dosage used	First individual FMS treatments: • 3×30 mg orally[30] • 75 mg retarded (Kern KU. Data on file. Personal clinical observations. 2011–2017) • 20% cream topically (Kern KU. Data on file. Personal clinical observations. 2011 -2017)	Prenatal lung maturation: 1 g IV[316] ARDS (children <1 year): up to 40 mg/kg/day[322] Atelectasis: 1 g IV[317] Gaucher's: 1,300 mg/day[79] Parkinson's: 1,050 mg/day[76] Individual reports (safe): • up to 3 g/day over 53 days[318–320] • oral 1.3 g/day over 33 days[321]
Treatment durations	First individual FMS treatments: 4–6 weeks	Clinically used treatment durations: 90 mg for 3 months[52] 2×75mg for 6 months[324] and 1 year[325] Ongoing trial: 225–1,050 mg/day for 52 weeks[76]

Note: Potentially helpful modes of action of ambroxol and reported dosage and treatment durations included.
Abbreviations: ARDS, acute respiratory distress syndrome; ASIC, acid-sensing ion channel; CNS, central nervous system; FMS, fibromyalgia syndrome; IV, intravenous; Na_v, voltage-gated sodium; NP, neuropathic pain; SNS, sympathetic nervous system; TTX-r, tetrodotoxin-resistant.

Table 3 Relevance of sodium channels and corresponding therapeutic approaches

Sodium channels	**Fibromyalgia**	**Ambroxol**
Sodium channels	Important[26,196,333]	Sodium-channel blockade[34–36]
Na_v1.7	Polymorphism found in severe FMS,[26] important in DRGs[196]	Na_v1.7 blockade[107,259]
Na_v1.8	Expressed in (damaged) small C-fibers[37–40,166–168,171] Important for sensitization[171,190,304,334,335] Important for cold pain[38,174] (as in FMS)[173] Gain-of-function mutations: FMS-like symptoms[170,171,230,234,236]	Na_v1.8 blockade[34,35]
Lidocaine (unspecific blockade)	Helpful[129–132,336] Not helpful[337,338]	40-fold more potent[36] 12-fold more specific for Na_v1.8[36]
Na_v1.7 and Na_v1.8 blocker		
Duloxetine	Helpful[157,238] Impact: blockade of Na_v1.7 and Na_v1.8 [240,241]	Na_v1.7 blockade[107,259] Na_v1.8 blockade[34,35]
Amitriptyline	Recommended [157,238] Impact: blockade of Na_v1.7[239,243,244] and Na_v1.8[244]	Na_v1.7 blockade[107,259] Na_v1.8 blockade[34,35]
Ibuprofen	Preferred by patients[157] Impact: blockade of Na_v1.7[253–255] and Na_v1.8 systemically[255] and topically[254]	Na_v1.7 blockade[107,259] Na_v1.8 blockade[34,35]
Gabapentin	Helpful (Cochrane review)[249] Impact: blockade of Na_v1.7[250,251]	Na_v1.7 blockade[107,259]
Pregabalin	Helpful[157,249] Effect Na_v1.7-associated[252]	Na_v1.7 blockade[107,259]
Tramadol	Second-line treatment[157] Impact: sodium-channel blockade	Sodium-channel blockade[34–36]

Abbreviations: DRGs, dorsal root ganglia; FMS, fibromyalgia syndrome; Na_v, voltage-gated sodium channels.

this could contribute to general hypersensitivity and chronic widespread pain.[84] The inflammatory components of FMS have also been regarded as an expression of mitochondrial dysfunction, and thus an improvement in mitochondrial function may be a new therapeutic approach.[85] In turn, ambroxol has an impact on mitochondria: it inhibits lipid peroxidation in hepatic mitochondria by 96%,[59] prevents toxic increase in mitochondrial membrane permeability,[60] and in animal models improves mitochondrial oxidative damage.[61]

Another investigation also pointed to mitochondrial dysfunction: stimulation of mononuclear cells of healthy subjects resulted, as expected, in significantly increased cytokine levels in contrast to unstimulated cultures. In FMS patients, however, the concentrations of most cytokines were lower. Behm et al[11] interpreted this observation as an impairment of cell-mediated immunity in FMS patients. On the other hand, there are findings that ambroxol could protect immunocompetent cells from dysfunction[86] and appears to strengthen cell-mediated immunity.[87]

Mast cells

In comparison to healthy subjects, patients with FMS have more mast cells in the skin.[53,88] The significance of this finding for the pathogenesis of FMS has been classified as unclear by

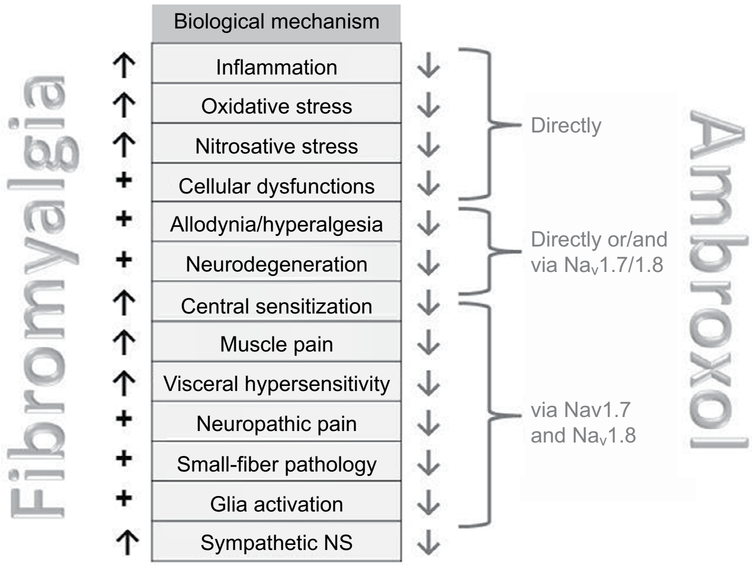

Figure 4 Mechanisms involved in fibromyalgia and influenced by ambroxol (see Tables 1–3).
Abbreviations: Na_v, voltage-gated sodium channels; NS, nervous system.

some authors,[88] whereas others have used this as a basis for classifying FMS as a mast cell-associated disorder.[53] If this latter interpretation were to hold true, the fact that ambroxol inhibits secretion from mast cells[54–56] would be of considerable importance. At least in pain models on ischemia/reperfusion, there is clearly a close relationship between cardiac mast cells and C-fibers.[89] Furthermore, mast cells play an important role in chronic urticaria, and in one study a surprising 70% of 126 urticaria patients also suffered from FMS. Torresani et al[90] discussed whether neuropeptides released owing to degranulation of increased numbers of mast cells in FMS patients may stimulate nerve endings, and chronic urticaria may thus occur as a result of skin neuropathology in FMS. Recently, it was demonstrated that cortiocotropin-releasing hormone and substance P are increased in FMS and stimulate release of IL6 and TNFα from mast cells.[91] Both IL6[44,46,47] and TNFα[44–46,48–52] are reduced by ambroxol. However, there are open questions remaining: therapeutic use of the mast-cell stabilizer ketotifen does not show significant differences between groups with regard to pain and Fibromyalgia Impact Questionnaire (FIQ) scores, which raises the question whether mast cells do play a major role in FMS.[88]

Chronic psychological, oxidative, and nitrosative stress

Chronic stress and cortisol

Since it is still not clear how chronic stress influences visceral and somatosensory pain regulation, both types of hyperalgesia were investigated in an animal model: the authors demonstrated that chronic stress also led to upregulation of the Na_v1.8 channel.[92] It was shown that both visceral and somatosensory hyperalgesia and the increased expression of Na_v1.8 normalized after 3 days without stress: this related to sodium channels in the dorsal root ganglion (DRG) neurons of those segments, which are responsible for the pelvic viscera.[92] This may for example explain the associated visceral symptoms in FMS, and in turn suggest a therapeutic approach using ambroxol with its selective Na_v1.8 blockade. This applies even more if FMS is considered a stress-mediated disorder,[5,93] in which the overexpression of Na_v1.8 is not further downregulated and a receptor blockade would gain even greater importance.

Since pain and fatigue as core symptoms of FMS are also characteristic of disorders with reduced cortisol levels, it has been hypothesized that there may also be reduced cortisol levels (caused by fatigue?) in FMS. Although glucocorticoid tests in 12 female FMS patients showed no reductions in daytime cortisol profile in comparison to 15 controls, they did however show reduced sensitivity of glucocorticoid-receptor function; this was considered a pathophysiologically relevant finding for FMS by Geiss et al.[94] In this context, the fact that the anti-inflammatory potency of ambroxol is comparable to dexamethasone[46,51,95] and beclomethasone[96] without requiring glucocorticoid receptors is not necessarily relevant, but nevertheless worthy of note.

Oxidative stress

The findings concerning oxidative stress in fibromyalgia are currently still inconsistent. In particular, it is not clear whether the disease is caused by oxidative stress.[97] Enhanced oxidative stress mediated by free radicals is however evident in FMS and leads to increased cytokine expression. There is much evidence that suggests that increased oxidative stress leads to increased severity of FMS symptoms.[81,97] In particular, a positive correlation has been observed between FIQ and increased lipid peroxidation.[81] Malondialdehyde is a toxic metabolite of lipid peroxidation, and significantly increased levels of this metabolite have repeatedly been found in patients with FMS.[22–24] Ambroxol inhibits this harmful lipid peroxidation.[59,98,99] Furthermore, the enzyme xanthine oxidase correlates with the severity of muscular pain in FMS[100] and is also reduced by ambroxol.[45] A similar relationship has been shown for other antioxidative substances: decreased levels of catalase have been shown for FMS,[80,81] and these levels are enhanced by ambroxol.[62,101] The same applies to glutathione peroxidase,[45] which is also decreased in FMS patients and enhanced by ambroxol.[80,81] There are apparently lower levels of the intracellular antioxidative enzyme superoxide dismutase in FMS patients;[23,24,80] ambroxol can also lead to increased levels of this enzyme.[45,98,101–104] Skin biopsies of FMS patients also show increased levels of oxidative metabolites that correlated with the severity of pain and inflammation.[57] Both are relevant for the development of peripheral nerve damage, which has also been observed in FMS and may be the cause of allodynia. Since investigations on DRG neurons of mice recently suggested that nociceptor hyperexcitability induced by oxidative stress is primarily mediated via sensitization of the ambroxol-inhibited $Na_v1.8$-channel type,[105] Schlüter and Leffler[106] investigated the influence of the strong oxidant chloramine T. They confirmed these findings, which were more pronounced for the $Na_v1.8$ than for the $Na_v1.7$ subtype, which however is also inhibited by ambroxol.[107]

In summary, the balance of oxidants and antioxidants appears to be disturbed in FMS, and increased levels of free radicals are possibly responsible for development of the disease.[24,80] Fibromyalgia can thus also be understood as an oxidative disorder.[24] Understandably, rheumatologists are requesting further investigations into the effects of radical scavengers,[100] and ambroxol is known to be one such scavenger.[44,60,62–65]

Oxidative stress and lipid peroxidation do not only occur in FMS and depression. Some of the products resulting from these processes are in addition predictors for neurodegeneration; this may be the reason for associations of both indications with neuropathic pain.[108] Oxidative damage of DNA may be important in this context.[109] As a strong radical scavenger[44,60,62–65] and inhibitor of lipid peroxidation,[59,98,99] ambroxol may thus counteract neurodegenerative changes during disease progression in FMS.

Both ambroxol and melatonin are able to protect from lipid peroxidation.[110] Melatonin levels that are too low may have a negative impact in FMS.[111] Since melatonin is one of the targets of the latest strategies in the development of drugs for FMS,[112,113] and this is based on being a radical scavenger that functions like a strong antioxidant,[114] the same may also apply to ambroxol.

Nitrosative stress

Nitrosative stress is caused by reactive nitrogen species, eg, nitrogen monoxide (NO) and its product peroxynitrite. These harmful and highly reactive nitrogen compounds are involved in cellular dysregulation. It is assumed that nitrosative stress is involved in neurological and inflammatory disorders. This has also been demonstrated for FMS.[84,115] It has been suggested that NO is involved in the pathophysiology of FMS,[97,116] may be responsible for pain sensitivity,[117] and correlates with pain severity.[118] In addition, NO levels correlate with the FIQ score.[119] On this basis, Cimen et al[120] have requested the search for inhibitors of nitric oxide synthase (NOS) for FMS treatment, since this enzyme catalyzes the (unfavorable) formation of NO. The same effect, however, is also achieved with ambroxol: the compound inhibits the production and activity of NO.[44,121–123]

Sex hormones

Since FMS primarily affects women, there is reason to presume that sex hormones play an important role. Estradiol (E_2) has a key function in pain modulation. The effects of E_2 are mediated via estrogen receptors (ERs).[124,125] ERs (ERα, ERβ) and $Na_v1.8$ may be expressed in DRG neurons. In knockout mice for ERβ, $Na_v1.8$ is upregulated,[124] and in addition voltage-gated sodium channels are inhibited by E_2.[125] In principle, hormone deficiency may thus contribute to hyperexcitability in fibromyalgia. Hormone-replacement therapy, however, does not lead to an improvement in symptoms,[126] and sex-hormone deficiency has not been demonstrated for FMS.[127,128] Nevertheless, ambroxol is able to inhibit experimentally upregulated $Na_v1.8$ sodium channels[34–36] or those sodium channels that are functionally insufficiently blocked by E_2.[34] The compound is an approximately 12-fold stronger inhibitor of $Na_v1.8$ than lidocaine and 40-fold stronger if neuronal sodium channels in general are considered.[36] Of note, lidocaine has already been used successfully for FMS.[129–132,336]

Muscular pain

Both peripheral and central sensitization processes are involved in the transition from acute to chronic muscular pain.[133–135] One of the currently leading theories suggests that acute stimulation of specific nociceptors binding isolectin B_4 (IB_4) may lead to long-term hypersensitivity of nociceptors. Consequently, a lasting increase in TTX-r sodium-channel activity (such as $Na_v1.8$) is required, in order to achieve long-term changes in intracellular signalling.[136] $Na_v1.8$ inhibition with ambroxol would in this case be a preventive approach. Recent studies again confirmed the importance of IB_4-positive muscular nociceptors for chronic muscular pain,[137,138] thereby confirming older and similar research results.[139,140] Tissue hyperacidity in muscles owing to ischemia and inflammation has a decisive impact on the initiation and progression of chronic muscular pain.[141,142] Acid-sensing ion channel (ASIC)-3 and transient receptor-potential cation-channel subfamily V, member 1 are involved in the activation of muscular nociceptors, the induction of central sensitization, and chronic muscular pain.[143–145] ASIC3 has been demonstrated to play a major role in triggering acid-induced chronic muscular pain.[139,146] Its activation again increased $Na_v1.8$ activity, with essential development of long-lasting hyperalgesia and chronic widespread muscular pain in a mouse model of fibromyalgia.[41] Since to date, ASIC3 cannot be specifically blocked, Chen et al[41] considered selective blockade of $Na_v1.8$ a good treatment option for chronic muscular pain with ischemic conditions.

According to their own reports, patients affected by FMS in the US[147] and Germany[148] had only minor benefit from anti-inflammatory treatment. Correspondingly, in their microdialysis investigations in muscles of FMS patients, Christidis et al[149] detected no changes in the proinflammatory cytokines IL1β, IL6, IL8, or TNFα. In contrast, another cytokine, MCP1, not only occurs with increased levels in the blood of fibromyalgia patients[150] but is also supposed to induce persistent muscular hyperalgesia and chronic sensitization.[151] Should this be of relevance for FMS, ambroxol may again be of therapeutic benefit, since it can contribute to a reduction in MCP1.[51,95,152] Muscular pain in FMS patients is also explained by mitochondrial dysfunction in muscular cells.[84] As just described, this could also be improved by ambroxol.[59–61] Furthermore, the ambroxol-reduced oxidative–toxic enzyme xanthine oxidase[45] correlates with muscular pain severity in FMS.[100]

Neuropathic pain and small-fiber pathology

The latest research on FMS pain has shown that at least in a subgroup of patients, a neuropathic component is involved.[67,153–155] Changes in small nerve fibers and a high PainDetect score suggest this,[156] even though this questionnaire has not been validated for the disease.[155] In a comparison of diabetic polyneuropathy with FMS, approximately 30% of patients showed an overlap of sensory profiles, whereas other distinct profiles were disease-specific.[156] Furthermore, it is noteworthy that many drugs used for the treatment of FMS[157] are also used for neuropathic pain.[158]

There is increasing knowledge in particular about changes in small nerve fibers. In this respect, Uçeyler and Sommer[159] and Doppler et al[160] considered it important to use the term "small-fiber neuropathology" and distinguish this from "small-fiber neuropathy". Interestingly, Doppler et al[160] demonstrated significantly reduced average axon diameters in skin biopsies of 32 FMS patients compared to 12 patients with small-fiber neuropathy and 40 healthy controls. It appears that quite different pathophysiological mechanisms lead to the development of small-fiber degeneration and/or regeneration.[66,161] In FMS, not only changes in peripheral small fibers but also in the eye (which belongs to the CNS) occur.[162,163] Controlled investigations with skin biopsies[67] and laser-evoked potentials[164] showed reduced intraepidermal nerve-fiber density in FMS patients compared to healthy controls, and thereby also support the theory of at least a partial neuropathic origin of pain. As mentioned earlier, we were able to report clinical efficacy of topical ambroxol for neuropathic pain in previous publications;[27–29,165] however, experimentally there is also no doubt that ambroxol exerts systemic effects as well.[34,69–71] In small-fiber neuropathy, primarily small unmyelinated peripheral neurons are damaged; in other words, nociceptive C-fibers of the skin primarily expressing $Na_v1.8$.[37–40,166–168] In animal models, approximately 50% of the C-fibers express just these $Na_v1.8$ channels that are inhibited by ambroxol,[166] and their numbers even increase under painful conditions.[167,168] In addition, at least in patients with pure small-fiber neuropathy, gain-of-function mutations of $Na_v1.8$ have been detected.[169–172] Furthermore, $Na_v1.8$ can be increasingly expressed in case of distal degeneration of small-diameter peripheral axons and thus contribute to central sensitization.[171] Owing to its mechanism of action, ambroxol can be expected to provide some protection from this type of sensitization in FMS.

Finally, and as an indication for neuropathic pain involvement, patients with FMS show low tolerance of cold water,[173] whereas the ambroxol-inhibited $Na_v1.8$ channel is of particular importance for cold pain.[38,174] In the animal model, ambroxol suppressed cold allodynia by approximately 75%.[69]

Central sensitization, allodynia, and hyperalgesia

Central sensitization

It is widely accepted among researchers that the biological component of FMS is associated with long-term or even permanent functional changes of the nociceptive nervous system.[175,176] A systematic review on central sensitization in fibromyalgia evaluated 13 studies concerning functional changes (via functional magnetic resonance imaging). Nociceptive stimuli led to more pronounced but otherwise comparable activation of the pain matrix in FMS patients compared to controls.[42] Eight studies investigating structural changes (via voxel-based morphometry) provided moderate evidence for a correlation between central sensitization and a decrease in gray matter in certain regions.[42] In their experiments with thermal stimulation, Vierck et al[177] demonstrated abnormally prolonged sensitivity in FMS patients, which again was interpreted as an indication of central sensitization and a specific influence of widespread chronic pain from deep somatic tissue. Visceral hyperalgesia, somatosensory hyperalgesia, and increased expression of $Na_v1.8$ are closely associated.[92] Correspondingly, $Na_v1.8$-selective antagonists (other than ambroxol) have analgesic efficacy in acid-induced chronic widespread-pain models[178] and lead to a reduction in allodynia and hyperalgesia[179] in animal models of neuropathic and inflammatory pain. Following experiments in a fibromyalgia animal model, Chen et al[41] thus generally considered selective $Na_v1.8$ blockers, one of which was ambroxol, as a good choice of treatment of chronic pain and for limitation of central sensitization.

Allodynia and hyperalgesia

Allodynia and hyperalgesia are common signs in FMS.[180–182] Sleep deprivation can cause these signs,[183] as well as oxidative stress, mitochondrial dysfunction, and inflammation, with the consequence of peripheral nerve damage.[57] Functional brain-imaging studies have provided compelling evidence for abnormal pain processing in FMS correlating with patients' hyperalgesia or allodynia.[184] FMS patients experience prickling and touch-evoked allodynia at the same frequency as patients with diabetic polyneuropathy.[156] Furthermore, FMS patients show lower heat-pain and cold-pain thresholds than controls,[185,186] and severe thermal allodynia following cutaneous heat exposure has been reported.[187] Systemic ambroxol, however, suppressed heat hyperalgesia by 100% in an animal model.[69]

Pain symptoms in FMS animal models are more likely associated with dysfunction of biogenic amine-mediated CNS pain control compared to pain due to nerve injuries.[188] However, rats in an FMS model showed hypersensitivity to tactile muscle pressure and cold stimuli. Once again in an animal model, ambroxol reduced cold hyperalgesia and mechanical allodynia by approximately 75%.[69] The observation that ambroxol also reduces mechanical allodynia in an experimentally induced inflammation in rats by approximately two-thirds[68] suggests that the antiallodynic analgesic effect is not necessarily restricted to neuropathic pain. It is indeed possible to reduce mechanical allodynia in monoarthritis pain with ambroxol by 50%.[69]

The $Na_v1.8$ channel is detected mainly in C- or Aδ-fibers and neurons of the posterior horn,[37–40] although it is also expressed in Aβ-fibers.[68,174,189–191] Since in chronic inflammation, which is also discussed for FMS, the excitability of $Na_v1.8$ is shifted to hyperpolarization, this contributes to allodynia, and a blockade using ambroxol should then have a particularly pain-relieving effect. For completeness, it should not go unmentioned that the intrathecal administration of ambroxol has also led to an antiallodynic effect in animal experiments.[68] Furthermore, simultaneous therapy with ambroxol reduces heat and cold hyperalgesia due to oxaliplatin in an animal model, which the authors felt to be transferable to humans.[192] In summary, there is plenty of evidence for a reduction in FMS hyperalgesia or allodynia following ambroxol treatment.

Sympathetic nervous system, glia, and dopamine

Sympathetic nervous system

One indication of sympathetic nervous system involvement in FMS was detected in a subgroup of obese female FMS patients by Okifuji et al.[193] They found a strong correlation between body-mass index and levels of the sympathomimetic epinephrine and IL6. The latter agent is reduced by ambroxol.[44,46,47] Investigations into heart-rate variability have shown persistent excessive sympathetic activity in FMS.[194] Norepinephrine injections can induce FMS pain.[195]

In 2009, Martinez-Lavin and Solano[196] presented a hypothesis on FMS in which sodium channels play a major role, and the authors suggested that sodium-channel blockers could become a therapeutic option for FMS pain. This renders the sodium-channel blocker ambroxol interesting for therapy: sodium channels localized in DRGs have a molecular gatekeeper function for impulses from peripheral nociceptors. Trauma, infection, or other factors may induce neuroplasticity via overexpression of sympathetic fibers and sodium channels in DRGs. The authors considered enhanced DRG excitability to play a key role in FMS pain. Since DRGs are potential sites of sympathetic–nociceptive short circuits, individuals who are genetically predisposed for sympathetic hyperactivity and those with inherent sodium channelopathies would be at risk of developing FMS. In addition, stressful environmental conditions in today's society could possibly contribute to sympathetic hyperactivity, and anti-inflammatory vagus-nerve activity might not be sufficient to counteract this. If FMS is interpreted in this context as a sympathetically maintained neuropathic pain syndrome, sodium-channel blockers gain importance as a therapeutic option for FMS pain.[196] At least, the sodium channel $Na_v1.8$, which is selectively blocked by ambroxol, is of importance in the sympathetic nervous system. Schofield et al[197] demonstrated that $Na_v1.8$ occurs on the sympathetic superior cervical ganglion and can be blocked. Facer et al[198] demonstrated the presence of $Na_v1.8$-immunoreactive sensory nerve fibers in the human myocardium, which are – interestingly with regard to sympathetic function – frequently closely associated with small capillaries.

Glia activation and dopamine

Apart from obviously enhanced sympathetic activity, FMS patients also have increased IL8 levels in cerebrospinal fluid,[199,200] which in principle can be reduced by ambroxol.[96,201–205] Kadetoff et al[200] interpreted their findings to be a result of FMS symptoms being mediated by sympathetic activity, rather than being dependent on prostaglandin-associated mechanisms, and considered this supportive of the hypothesis of glia-cell activation in response to pain mechanisms.[200] Interestingly, intrathecal administration of ambroxol leads to an antiallodynic effect in an animal model without having an impact on peripheral swelling caused by inflammation.[68] Moon et al[71] also concluded that after intrathecal administration of ambroxol that early treatment with an $Na_v1.8$ inhibitor may be an important factor in the clinical management of chronic mechanical allodynia during inflammatory or ischemic pain.[71]

Enhanced levels of IL8 have the potential to activate glia cells.[206] Activated glia cells in turn can also produce new IL8,[207] which again promotes sympathetically maintained pain.[208] In addition, activated glia cells can produce IL1β as a result of proinflammatory stimuli,[209,210] and IL1β is also reduced by ambroxol.[44,45] Recent research has shown that glia cells maintain neuronal hypersensitivity in DRGs by releasing substances that also act on the immune system.[211] In addition to peripheral changes, persistent glial activation with resulting central sensitization is also of importance in FMS, which in turn is activated by cytokines from repeated tissue injury.[17,212] Albrecht et al[213] considered glial activation in the brains of FMS patients, which was demonstrated via imaging procedures (positron-emission tomography and magnetic resonance imaging) to be being important in the pathophysiology of the disease. In another investigation, 126 fibromyalgia patients were genotyped and subgroups formed with regard to their binding affinity to translocator protein (TSPO), which is upregulated during glial activation. Those patients with high TSPO-binding affinity reported significantly more pain and FMS symptoms, which again supports glia-related mechanisms in FMS.[214] This fits with the observation that naltrexone, an inhibitor of microglial activity in the CNS, reduced FMS symptoms in some patients in a small pilot study.[215]

A permanent and robust increase in microglia population also contributes to an overexpression of α-synuclein, a small soluble protein in the brain of vertebrates which, among other actions, regulates the release of dopamine.[216] Su et al[217] demonstrated that α-synuclein in addition also activates microglia, thereby contributing to the release of proinflammatory molecules. This finding has been supported by other authors.[218] The release of α-synuclein from affected neurons was also increased in an animal model of CNS injury with ischemia–reperfusion, thereby mediating microglia activation.[219] The protein has neurotoxic effects, and not only leads to the microglia activation described but also to increased dopaminergic neurodegeneration.[220] Research on the pathophysiology of fibromyalgia is increasingly focusing not only on glia activation but also on the neurotransmitter dopamine. Experimental induction of FMS has demonstrated decreased dopamine levels in both the brain and the spinal cord.[221] Imaging procedures, however, have pointed to dopamine dysfunction as an important factor in increased pain sensitivity in FMS.[222] Other authors have also considered dopamine an important neurochemical moderator of FMS pain perception, since their data suggested interrupted dopaminergic neurotransmission in FMS.[223] It is thus plausible that dopamine receptors are investigational targets for new FMS medications.[113] It should be pointed out that in this respect, ambroxol leads to a reduction in α-synuclein,[224] ie, reduces just that protein that contributes to both glia activation and dopaminergic neurodegeneration.[220] For this reason, the medication has also been considered for the treatment of Parkinson's disease.[74–76,224]

Neurodegeneration and neuroregeneration

A systematic review on imaging studies revealed indications of structural changes in the CNS of fibromyalgia patients.[42]

The neurodegenerative findings of small-fiber neuropathology mentioned earlier are not restricted just to the peripheral nervous system either, but have also been reported for the cornea (cranial nerve V)[162] and axonal nerve injury early in the progression of the disease in the retina of FMS patients,[163] which belongs to the CNS. It is generally accepted that the regenerative capacity of injured nerves in the CNS is markedly worse than in the peripheral nervous system. Therefore, it is remarkable that neuroregenerative properties in the CNS have recently been described for ambroxol.[225] During a systematic genetic search for suitable treatment options promoting regenerative neuronal growth, Chandran et al[225] found that ambroxol was not just the only one of the tested substances causing eight gene expressions in treated DRG neurons, but also enhanced axonal sprouting from these. Furthermore, they were able to demonstrate real neuroregeneration in the CNS by ambroxol in an optical nerve model in vivo: studies using knockout mice confirmed that systemically administered ambroxol significantly and morphologically improved regeneration of the optic nerve.[225] It has to be pointed out, though, that despite the fact that ambroxol obviously crosses the blood–brain barrier,[79,226] brain levels could be too low to cause relevant effects under currently used therapeutic dosages.[227] This reduces potential side effects, and also a therapeutically desired effect. Whether the mother substance bromhexine, which definitively crosses the blood–brain barrier without CNS side effects,[228] could be of additional benefit remains unanswered.

At least in ischemia-induced neurodegeneration, reactive oxygen species have a key function, and ambroxol is able to contribute to the reduction of such ischemia-caused nerve injury.[229] Oxidative stress and lipid peroxidation occur not just in fibromyalgia and depression. Some of the products resulting from these processes are also predictors of neurodegeneration.[108] As a strong radical scavenger and inhibitor of lipid peroxidation, ambroxol should under these circumstances counteract neurodegenerative changes during the progression of FMS. This effect of ambroxol has been demonstrated at least for polyneuropathy caused by oxaliplatin.[192] Oxaliplatin also leads to an increase in inflammatory mediators and oxidative stress, and is thus peripherally neurotoxic. Simultaneous treatment with oral ambroxol in these animal models reduces relevant neuropathic pain, and as a result decreases heat and cold hyperalgesia, and both of these symptoms have also been reported for FMS.[154,156,185,186] The authors considered these results transferable to humans.

Sodium channels

There is some evidence that sodium channels are important in FMS. In an investigation of 73 female FMS patients, genetic $Na_v1.7$ polymorphism was associated with severe fibromyalgia.[26] The receptor is assumed to play an important role in pain transmission in DRG neurons in FMS.[196] $Na_v1.7$ subtypes,[170,230–233] as well as $Na_v1.8$ mutations,[171,234] are also associated with small-fiber neuropathy, and at least one small-fiber pathology appears to be present in a subgroup of FMS.[159,160] Although there have been reports of $Na_v1.7$ gain-of-function mutations and even more evidently hypothalamic dysfunction, it is not known whether or not this channel subtype plays a functional role in the hypothalamus with regard to external stressors in man. At least experimentally, however, it can be demonstrated that $Na_v1.7$ is upregulated in the CNS in parallel with osmotic stress[235] and that oxidative stress leads to sensitization of $Na_v1.8$.[106] In gain-of-function mutations of the *SCN10A* gene, which encodes for $Na_v1.8$, symptoms with diffuse painful sensory neuropathy, autonomic symptoms and gastrointestinal dysfunction[170,171,234,236] resemble FMS symptoms and are associated with hyperexcitability of DRG neurons.[230] Selective sodium-channel blockers are currently unavailable for routine clinical practice.[237] As presented herein, quite a few medications used for fibromyalgia cause (among other actions) sodium-channel blockade, even though this is aspecific.

More than 500 randomized controlled trials (RCTs) on the treatment of fibromyalgia were already available in 2008. The strongest recommendations of several medical societies were for various antidepressants.[238] It is remarkable that many tricyclic antidepressants, selective serotonin-reuptake inhibitors, and serotonin–norepinephrine reuptake inhibitors also block sodium channels.[239] For instance, duloxetine is beneficial for FMS[157,238] and blocks both $Na_v1.7$ and $Na_v1.8$.[240,241] The sodium-channel blockade of duloxetine is stronger than that of venlafaxine, which in turn was only attributed minimal effects in a systematic review.[242] Amitriptyline, which has received a strong recommendation for FMS,[157,238] also blocks $Na_v1.7$[239,243,244] and $Na_v1.8$,[244] or rather generally TTX-r channels (to which $Na_v1.8$ belongs) in trigeminal neurons, DRG neurons, and gastrointestinal neurons.[245–247] On the other hand, paroxetine shows less effect in FMS,[157,248] and in comparison to amitriptyline only blocks $Na_v1.7$ at high concentrations.[239] Furthermore, gabapentin, which was recommended in a data analysis by Cochrane[249] also blocks $Na_v1.7$,[250,251] and pregabalin, which was also classified as beneficial,[157,249] reduces paroxysmal neuropathic itch in patients with a variant of the

SCN9A gene, which encodes for $Na_v1.7$.[252] Even ibuprofen, which is often preferred by patients,[157] blocks the channel subtypes $Na_v1.7$[253–255] and $Na_v1.8$ after systemic[255] and topical administration.[254] Finally, tramadol, which is recommended as second-line treatment,[157] also blocks sodium channels.[256,257] An interesting fact in this respect is that at least peripheral analgesia with opioids is partly mediated via μ-receptors on primary afferent $Na_v1.8$-positive neurons.[258]

Although much evidence points to the importance of sodium channels in FMS and promising RCTs have been conducted, the relevance of sodium channel-blocking antiepileptic drugs cannot be confirmed: in a systematic review, Wiffen et al[249] found no valid indications that the sodium-channel blockers of this group of substances achieved above-average therapeutic results in FMS. It tends to be forgotten, however, that to date generally, no specific analgesics for the blockade of the main targets $Na_v1.7$ and $Na_v1.8$ are available for treatment, and for this very reason could not be assessed in this review. Thus far, none of the compounds used for neuropathic pain (including local anesthetics, antidepressants, and antiepileptics) shows relevant selectivity for $Na_v1.8$ that would be comparable to ambroxol.[34,35] Should the blockade of $Na_v1.8$ and/or $Na_v1.7$ be an important treatment approach for FMS, efficacy of ambroxol is very likely: not only $Na_v1.8$ but also $Na_v1.7$ is selectively blocked by ambroxol,[107,259] and this blockade is even more pronounced in man than in rats.[107]

Inflammatory mediators

Cytokines

Independent of sodium-channel blockade or antineuropathic effects, ambroxol should be able to reduce nociceptive pain via its anti-inflammatory properties. This has also been reported by us for topical ambroxol in a case series of pain patients.[29] In addition, it has been shown in humans for acute sore throat[260,261] and experimentally demonstrated.[32,33,46,68,69,262] Ambroxol exerts its comprehensive anti-inflammatory properties, for example, via inhibition of many proinflammatory cytokines.[32]

The general importance of cytokines in the induction and maintenance of pain has been well demonstrated in both animal models and pain syndromes in humans,[263] including FMS.[12,13,264] Cytokines can also contribute to the origin of pain in the CNS, and spinal cytokines can exert an external impact on peripheral pathology by influencing the efferent neuronal system, with effects on peripheral tissue.[265] They are also important mediators of neuropathic pain,[266–268] which is also reduced by ambroxol (as already reported). Cytokines also have an impact on changes in the hypothalamic–pituitary–adrenocortical axis,[269–271] and thereby on clinical symptoms, such as hyperalgesia, fatigue, sleep disorders, allodynia, adrenocortical hormone-associated disorders, stress responses, anxiety, muscular pain, and cognitive dysfunction;[13,200] all these are symptoms associated with FMS.[19–21] The diverse and well-documented impact of ambroxol on cytokines is likely to be of major relevance.

Interleukin 6 and interleukin 8

In particular proinflammatory and thus pain-inducing IL6 and IL8, which are both reduced by ambroxol, have clinical relevance in FMS. During the past 10 years, approximately 100 of 140 studies on FMS have demonstrated changes in inflammatory mediators and associated these with the pathogenesis and clinical signs of the disease. Several studies observed increased serum levels of IL6[14,199,200,272] or IL8.[199,200,273–275] A systematic review conducted in 2011 reported evidence for higher serum levels of these cytokines, as well as for IL1RA in FMS, but no confirmed changes in IL1β, IL4, IL10, MCP1, or TNFα.[12]

Even before the observation of a real correlation of the intensity of the disease with IL6 und IL8 levels, these were repeatedly reported as being associated with the clinical symptoms of FMS.[13,276,277] For instance, Mendieta et al[276] demonstrated that both IL6 and IL8 correlated with clinical psychiatric scores, and considered these interleukins as particularly constant inflammatory mediators in FMS, with their levels significantly correlating with the severity of symptoms.

However, serum concentrations do show large variability, as demonstrated in a systematic analysis by Uçeyler et al.[12] In particular, a disturbed balance of proinflammatory and anti-inflammatory cytokines is likely to play a role in the origin and maintenance of FMS-related pain.[263] Their pathophysiological role continues to be disputed, though.[12,16,17] In contrast to other authors, Ranzolin et al[278] did not discover differences in IL6 or IL8 in FMS patients compared to healthy controls in a recent prospective controlled study. Reasons for many partially contradictory findings concerning cytokines are multiple impact factors, such as circadian rhythmicity and influences from depression, physical activity, and infections, which were frequently not clearly assessed in the studies. In addition, drugs can have an impact on cytokines, such that cytokines vary in subgroups or during the progression of the disease. In a systematic investigation of ambroxol for the treatment of fibromyalgia, these factors will definitely need to be considered, at least for this partial effect of the compound.

Interleukin 6

During the last 10 years, numerous studies have demonstrated higher serum levels of IL6 in FMS,[14, 91,199,200,272] and this has been confirmed in a systematic review and meta-analysis.[12] Since IL6 not only has algesic effects but is also involved in the development of hyperalgesia,[279] fatigue, and depression,[13,14] it can be assumed to have a role in the modulation of FMS symptoms.[208] As it is very difficult to limit neuronal hyperexcitability caused by IL6, this interleukin obviously plays a major role during the chronification process and in the poor response of some pain conditions to treatment.[280] With robust data on increased IL6 levels in FMS, there are also equally robust data confirming that ambroxol reduces both the release and levels of IL6.[44,46,47,205] In a model on acute lung injury, this was demonstrated with comparable significance to dexamethasone-treated animals.[46]

Interleukin 8

In the aforementioned review, Uçeyler et al[12] also demonstrated higher serum and plasma levels of IL8. These findings were repeatedly confirmed thereafter.[199,200,273,274,277] Ang et al[150] found a significant correlation of increased IL8 levels with pain severity using the Brief Pain Inventory (BPI): they were able to correlate each change in pain intensity according to BPI with a corresponding increase in IL8. Using a highly sensitive method, Xiao et al[277] supported the assumption of inflammatory changes in FMS by demonstrating an elevated level of the inflammatory marker CRP in 105 FMS patients compared to 61 healthy controls. The elevated CRP values also showed a significant correlation with IL8 levels. Furthermore, Sturgeon et al[93] demonstrated a significant correlation between IL8 levels and pain catastrophizing, anxiety, and postmenopausal depression. IL8 was also associated with pain and sleep disorders.[273] In a comparison of cerebrospinal fluid findings in rheumatoid arthritis and FMS, Kosek et al[199] demonstrated higher IL8 levels in FMS patients. Kadetoff et al[200] also demonstrated higher cerebrospinal fluid and serum concentrations of IL8 in fibromyalgia, an overall constellation that the authors interpreted as an expression of sympathetic activity. In an animal model, Moon et al[71] correspondingly showed that intrathecal ambroxol inhibited mechanical allodynia and thermal hyperalgesia in a dose-dependent manner. It can be assumed that a reduction in IL8 is involved: in vitro as well as in vivo, both the release and detectable concentrations of IL8 are reduced by ambroxol, a fact that has been repeatedly shown.[47,96,201–205] This is probably an important finding concerning this “perhaps most important interleukin” in FMS.

IL1-receptor antagonist

IL1RA is an inhibitor produced by the body that slows down and finally stops the action of the proinflammatory IL1 and IL1β by binding at their site on the IL1 receptor. Increased serum levels of IL1RA in FMS have been demonstrated in many studies;[12,199] however, the proinflammatory interleukins “to be regulated” – IL1 and the highly reactive IL1β – do not at all appear to show elevated serum levels in FMS.[12,200] In contrast to this, however, Imamura et al[281] detected similarly elevated levels of IL1β in a comparison of FMS patients to osteoarthritis patients, with comparable duration of disease and pain intensity. Using questionnaires and plasma analyses of 50 FMS patients, Menzies et al[19] demonstrated a negative correlation between subjective stress and IL1β levels. Therefore, possibly just the fact that no elevated levels of IL1 or IL1β can be detected is an expression of severe FMS symptoms or for long duration of the disease. For instance, this may be the reason that elevated levels of IL1β in skin have indeed been detected, but only in a subgroup of FMS patients.[43] The impaired balance between IL1 and IL1RA remains to be clarified. It is a fact, however, that ambroxol has a major impact: it has been well demonstrated to reduce IL1[44,45,48,51] and IL1β,[44,45] and thus should have a positive preventive effect, at least in cases of initially elevated levels, if present.

Interleukins 4 and 10

Investigations have shown decreased levels of the anti-inflammatory and thus “analgesic” cytokines IL4 and IL10 in FMS in comparison to healthy controls.[18] In a 2011 review, however, the same research group could not detect clear evidence of serum differences in these two interleukins.[12] Mendieta et al[276] also recently reported no relevant changes in serum levels of IL10 in FMS.

In contrast to this, other authors have demonstrated elevated IL10 levels[13,278,281,282] and a significant correlation of these with FIQ scores.[283] IL10 is also increased in the cerebrospinal fluid of FMS patients in comparison to patients with rheumatoid arthritis.[199] Under ambroxol treatment in experimental stimulation of human alveolar macrophages, IL10 was not elevated, in contrast to IL12,[87] and the same applied after bacterial stimulation.[284] Ambroxol thereby promoted a reduced cytokine response after exogenous inflammation and strengthened cell-mediated immunity by shifting the “local balance” toward IL12.[87] Following exposure to allergens in an artificially sensitized respiratory tract in an animal model, however, ambroxol induced an increase in IL10 in a “protective” manner.[285]

Yigit et al[286] genotyped 300 FMS patients and 270 healthy controls with regard to IL4 for specific polymorphism of the *IL4* gene. They detected highly significant differences, suggesting that IL4 may be a suitable genetic marker for FMS. Investigations of various authors, however, led to inconsistent results by reporting decreased IL4 levels,[18,287] no change in IL4 levels,[288] or increased IL4 levels[199] in FMS. In an investigation on human mast cells, even very low dosages of ambroxol inhibited anti-IgE-induced release of IL4.[54]

Monocyte chemotactic protein 1

MCP1 (formerly called CCL2) in human monocytes acts in an anti-inflammatory fashion by inhibiting the development of proinflammatory cytokines. Not only have some investigations on fibromyalgia shown elevated levels of MCP1,[150,274] but it also induced dose-dependent chronic mechanical hyperalgesia for up to 6 weeks in an animal model.[151] In their interpretation of the results, the authors suggest that MCP1 induces persistent muscular hyperalgesia and thereby chronic sensitivity toward other proalgesic substances. Ang et al[150] reported elevated levels of MCP1 in FMS and demonstrated significant correlations of each change with pain severity measured using the BPI. They thus presumed that MCP1 is involved in the pathogenesis of FMS. MCP1 was also elevated in 25 FMS patients with an "altered stress response" compared to healthy controls.[274] There is, however, possibly a negative clinical correlation with subjective, actually perceived stress.[19] The importance of this finding has been emphasized by genetic investigations, in which markedly elevated MCP1 levels were detected in an FMS subpopulation with a specific mutation.[289]

If MCP1 is indeed of importance in FMS, patients might benefit from treatment with ambroxol. In an animal model, inhaled ambroxol reduced MCP1.[51,95] The effect of ambroxol by inhalation at 7.5 mg/mL was comparable to 0.5 mg/kg intraperitoneal dexamethasone. Again, potent effects comparable to cortisone have been demonstrated.[95] In another animal model with several control groups, ambroxol was also able significantly to reduce experimentally elevated MCP1 for 28 days.[152]

Inflammasomes

Recent studies identified inflammasomes, cytosolic protein complexes in macrophages and neutrophil granulocytes, as promoters of classical cytokine-mediated inflammatory processes.[290] The NLRP3 inflammasome is assumed to be activated in FMS[291,292] and is considered a new therapeutic target.[293] Inflammasomes are obviously inhibited in their activity if reactive oxygen species ("oxygen radicals") are reduced[290] and activated by mitochondrial dysfunction,[292] both of which are presumed to be present in FMS.[57] Since ambroxol is a strong radical scavenger[44,60,62–65] and improves mitochondrial dysfunction,[59–61] it should also have an impact on this newly described pathomechanism.

Interleukin 13, interleukin 5, and immunomodulation

Following secondary data analysis, Sturgill et al[287] reported a remarkable reduction of IL13 in FMS patients. This interleukin is produced by T lymphocytes, stimulates the differentiation of B lymphocytes, and is generally considered a central mediator in allergic reactions. In cases where decreased IL13 levels have to be discussed as missing anti-inflammatory components, ambroxol would apparently exacerbate this condition: the release of IL13 is reduced by ambroxol.[54] Ambroxol also reduces IL13 if administered prior to experimentally produced hyperreactivity of the airways and subsequent exposition to allergens; however, this is not the case if administered afterward. Interestingly, overall this had a beneficial and protective effect.[285] This applies similarly to IL5, which has a positive chemotactic action on eosinophilic granulocytes: Sturgill et al[287] also demonstrated a reduction of IL5 in FMS. Ambroxol also has an inhibiting effect concerning IL5, and if administered prior to provocation in an animal model, suppressed hyperreactivity and airway eosinophilia and reduced inflammation of subepithelial regions.[285] The relationships described raise the question of whether potent inhibition of the release of IgE-dependent mediators[294] and immunomodulatory cytokines from basophilic granulocytes by ambroxol,[54] as well as the immunomodulatory significance of Na_v1.8 sodium-channel inhibition by ambroxol,[295] are important in FMS and warrant further investigation.

Symptoms associated with fibromyalgia

Patients with fibromyalgia also suffer from hypersensitive visceral organs. Symptoms of overactive bladder,[296] for instance, occur more frequently in fibromyalgia patients and depend on the severity of the disease. These can be assessed using the fibromyalgia bladder index.[297] Patients with chronic interstitial cystitis or painful bladder disorders, on the other hand, show an above-average presence of fibromyalgia.[298] According to investigations on rat bladders by Drewa et al,[299] ambroxol is also able to suppress bladder contractions; they thus considered the compound a therapeutic option for the treatment of overactive bladder.

In similar fashion, irritable bowel syndrome (IBS) is also associated with fibromyalgia: FMS patients suffer more often from this disease,[300] and FMS is found more often in patients with IBS.[301] Besides new insights concerning the potential importance of $Na_v1.1$ for IBS,[302] especially the $Na_v1.8$ receptor, which is selectively blocked by ambroxol, is again of importance: in general, investigations with $Na_v1.8$-free mice and $Na_v1.8$-inhibiting compounds showed lower (also visceral) hyperexcitability or a reduction of hyperexcitability under treatment.[68,174,178,179,303–306] Knockout mice without the $Na_v1.8$ receptor not only show little visceral pain but also no referred hyperalgesia whatsoever following stimuli in the colon.[307] Furthermore, $Na_v1.8$ mutations can be associated with gastrointestinal dysfunction.[234] Since in animal models particularly, colon DRG neurons exhibit $Na_v1.8$-mediated increase in activity of the sodium channels, Hu et al[308] considered this mechanism specific for chronic visceral pain and IBS. Selective $Na_v1.8$ blockade (such as by ambroxol) is thus considered clinically beneficial for visceral pain.[309]

According to a review, major influence of the sympathetic rather than the parasympathetic nervous system has been deemed responsible for fibromyalgia-associated symptoms,[310] again with sequelae that might be addressed with ambroxol and have already been discussed elsewhere. Another association that is clinically not quite as important, but nevertheless fits into the concept is the fact that FMS patients more frequently suffer from dry eyes, and the prevalence of FMS in patients with Sjögren's syndrome is increased by a rate of 12%–31%.[311–313] Ambroxol leads to an increase in tear-fluid secretion[314] and can improve sicca symptoms.[315]

Safety, dosage, and onset and duration of effect

In vitro, the onset of $Na_v1.8$ blockade by ambroxol starts within a few seconds, is concentration-dependent, and fully reversible.[34] In paraplegic rats, hypersensitivity to static mechanical stimuli was reduced after approximately 30 minutes for approximately 3 hours.[70] In earlier topical treatments, the effect reported by patients persisted for well over 6 hours.[27,29] The anti-inflammatory effect should increase over time.

In most countries, ambroxol has been sold as an over-the-counter drug for decades, owing to its good safety profile, and in 2015 the European Medicines Agency reassessed the clinical benefit:risk ratio of the drug. The selective sodium-channel blockade of the $Na_v1.8$ channel, which is only insignificantly expressed in the heart and the CNS, is in this case clinically beneficial. After systemic administration, ambroxol was also safe: even intravenous administration of 1 g (in order to boost prenatal lung maturation and for the treatment of atelectasis) is well tolerated.[316,317] There are individual reports of dosages of up to 3 g per day over 53 days[318–320] and oral administration of 1.3 g ambroxol per day over 33 days.[321] In a recent pilot study, ambroxol was used orally at dosages of 25 mg/kg/day up to 1,300 mg/day for Gaucher's disease and showed good safety and tolerability,[79] and in an ongoing study it is being used at 1,050 mg/day for Parkinson's disease.[76] Even in an RCT with children under 1 year of age with acute respiratory distress syndrome, no adverse events were noted with ambroxol up to 40 mg/kg/day.[322]

With its good bioavailability of about 80%[323] and plasma levels linearly correlated with oral dosage,[69] dosages very likely could be used tenfold higher (or even more) than actually used (up to 120 mg/d) for potential systemic trials for the treatment of fibromyalgia pain without risk. As many ambroxol effects apart from selective $Na_v1.8$ sodium-channel blockade develop more intensely over a longer period, we consider treatment for more than 4–6 weeks desirable before evaluation. However, this should not be a problem, because ambroxol has already been administered clinically at 90 mg for 3 months[52] and even at 75 mg twice daily without any problems for 6 months[324] and also at 75 mg twice daily for long-term treatment of 1 year.[325] A clinical trial investigating the treatment of FMS with ambroxol could even use a design comparable to an ongoing study, which is designed for 52 weeks using 225–1,050 mg/day for another indication.[76]

Conclusion

Overall, we think potential RCTs with FMS patients should examine the impact of ambroxol on pain, hypersensitivity, and inflammation at dosages higher then yet approved for the over-the-counter market and for at least 6 weeks. An increasing effect should be expected and possibly could be evident clinically not before two weeks of treatment. An impact on dysfunctional descending pain pathways should not be expected, so patients with a clear response to a medication for this (indicating this special origin of pain perception) might possibly report less benefit. As it is surprising that the single substance ambroxol has so many unexpected effects on FMS-related mechanisms, the chemical properties (eg, structure and affinity) and related substances (eg, the mother substance bromhexine) could also be worth examining further.

Summary

Fibromyalgia appears to present in subgroups concerning biological pain induction with primarily inflammatory,[12,13,264] neuropathic/neurodegenerative,[153–155] sympathetic,[193,194,196] oxidative,[24,81,97] or muscular factors[84,132,134] and/or central sensitization.[42,175,176] On the basis of this hypothesis, fibromyalgia treatment with ambroxol should be systematically investigated, since this compound is the only treatment option used thus far that has the potential to address not just individual but all of the aforementioned aspects of pain. Nevertheless, at this point, the evidence base for ambroxol is currently not strong enough for clinical recommendation.

Disclosure

In the past 3 years, KUK has worked as a consultant and/or speaker for the following companies (*offering ambroxol): Astellas, AstraZeneca, Bionorica, Berlin Chemie,* Boehringer Ingelheim,* Betapharm, Genzyme, Grünenthal,* Hexal,* Indivior, Kyowa Kirin, Lilly, Mundipharma,* Ratiopharm,* and Sanofi.* MS reports no conflicts of interest in this work.

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