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Mechanism of Action of Indomethacin in Indomethacin-Responsive Headaches

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Abstract Indomethacin, as a member of the non-steroidal anti-inflammatory drug class, plays a special role in the treatment of headaches. By definition, it is completely efficacious in the treatment of the primary headache disorders paroxysmal hemicrania and hemicrania continua. Therefore, indomethacin is also used as a tool for differential diagnosis in headache clinics. Indomethacin has a clear action as a cyclooxygenase inhibitor. Additional mechanisms and interactions with cell signaling pathways and inflammatory pathways are considered in this article. However, it is not known what mechanism or interaction with pathophysiological mechanisms is the key to indomethacin's specific pharmacology in headache therapy. Focusing on headache therapy, we summarize the current knowledge of pharmacology, treatment options, and recommendations for the use of indomethacin in primary headaches. New findings from the field of headache research, as well as from Alzheimer's disease and cancer research on the pharmacological actions of indomethacin and their potential implications on the pathophysiology of indomethacin sensitive headaches, are discussed.

Keywords Indomethacin · Headache · Hemicrania continua · Paroxysmal hemicrania · TAC · Trigeminal autonomic cephalalgia · NSAID · Non-steroidal anti-inflammatory drug · Mechanism · NO · Nitric oxide · COX · Cyclooxygenase

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Introduction

The list of medical indications for the use of indomethacin is long, thereby indicating that it is interacting with mechanisms that are central to many medical conditions. Its potent inhibitory effect on the synthesis of prostaglandins is important for anti-inflammatory effects, including fever, pain and swelling reduction. The production of prostaglandins is inhibited via the inhibition of cyclooxygenases (COX) 1 and 2 and is essential for most of the non-steroidal anti-inflammatory drugs (NSAIDs). The indications for NSAIDs, and in particular indomethacin, include arthritis, fever, various headache syndromes, and dysmenorrhea. Indomethacin is also used for closure of patent ductus arteriosus. It has become a challenge for recent research to classify the different NSAIDs only by their actions on cycloxygenase 1 and 2, since some of the observed effects are insufficiently explained by the known mechanisms. By employing models of diseases with a known diverse effect of NSAIDs, recent studies have attempted to identify further mechanisms of action of these drugs that are relevant to the specific pathophysiology of the condition being studied. The latest results from investigations, including headache models as well as models from cancer and Alzheimer's disease research, are discussed, focusing on the new findings and implications relevant to headaches, particularly indomethacin sensitive headaches. Known limitations for the use of indomethacin, such as the adverse effects especially on peptic ulcer, are discussed elsewhere.

Indomethacin in Headache Therapy

Current Recommendations for the Use of Indomethacin in Primary Headaches

On the basis of the treatment recommendations published by the European Federation of Neurological Societies (EFNS), the use of indomethacin is not explicitly recommended as an

acute or prophylactic first line therapy for either migraine or tension-type headache [1, 2]. Whilst indomethacin is the first line therapy in the treatment of paroxysmal hemicrania, it is not recommended for use in cluster headache or short-lasting neuralgia with unilateral tearing (SUNCT). These headaches and the so called probable forms are the other headache entities within the group of trigeminal autonomic cephalalgias (TAC), as classified by the international classification of headache disorders (ICHD II) [3]. The ICHD II criteria require an obligatory effect of indomethacin in the treatment of paroxysmal hemicramia to make the final diagnosis. Sufficient doses of indomethacin (≥150 mgd^{-1} orally/rectally or ≥100 mgd^{-1} intravenously) have to be used for acute therapy, though the therapeutic effect can often be maintained by using smaller doses [4]. Although hemicraina continua is classified in the group of "other primary headaches" [4], the same treatment recommendations and requirements as for paroxysmal hemicrania apply for hemicrania continua, meaning that the diagnosis of either one of these headaches can only be made if there is complete response seen after a trial of a sufficient dose of indomethacin.

For other headache disorders classified in the group of "other primary headaches", such as primary stabbing headache, primary cough headache and primary exertional headach, indomethacin is also recommended as treatment of first choice [5•]. However, this is somewhat problematic, since there are no data from large clinical trials available that would allow level A recommendations. Therefore, the recommendations for most of these headache disorders are only level C and based on small trials or clinical observations. Primary stabbing headache usually does not demand any treatment because of the very short duration of attacks; if, however, the frequency of attacks is very high, the use of indomethacin has been reported to be efficient [6, 7]. In primary cough headache, indomethacin and naproxen are recommended for treatment [5•, 8–10]. Indomethacin is also successfully used in the treatment of primary exertional headache as an acute treatment or as a short term prophylaxis, with 25–30 mg 1 h before physical activity or as ongoing prophylaxis (25–50 mg per diem) [5•, 11, 12]. Indomethacin is efficaceous in primary headache associated with sexual activity as a short term prophylaxis [5•, 13, 14]. Indomethacin is not the drug of first choice for the acute treatment of hypnic headache (two negative case reports for indomethacin treatment [15, 16]). Whilst the first choice treatment is lithium, and flunarizine is used as a second choice drug, members of the NSAID group, as acetylsalicylic acid, paracetamol and ibuprofen are often used [5•, 16–21]. However, indomethacin is recommended as a drug of second choice in the prophylactic treatment of hypnic headache [5•, 17, 22–25].

As mentioned earlier according to the ICHD II criteria [4], patients can only be diagnosed with hemicrania continua or paroxysmal hemicrania if they are responsive to treatment with indomethacin. However, this criterion was challenged repeatedly by publications where patients were diagnosed with the clinical features of one of these headache entities, but were lacking the responsiveness to indomethacin. Understanding the ICHD II as a tool for research, it is, however, not necessary to change the classification for hemicrania continua or paroxysmal hemicranias. In fact, taking out the criterion of indomethacin responsiveness of these headaches would even lead to a loss of specificity of the ICHD II criteria; hereby this might even make it more difficult to differentiate the specific pathophysiology of these disorders, since false positive diagnoses would be detrimental to future research if they would enter studies of hemicrania continua or paroxysmal hemicrania.

A subclassification of these headache disorders in indomethacin responsive and non-responsive might help to conserve the specificity of the classification, but Goadsby and Lipton, taking up on the finding of this relatively large group of patients with symptoms resembling the indomethacin responsive headache disorders without the beneficiary effect of the drug, therefore proposed modified criteria of hemicrania continua [26].

Alternatives to Indomethacin in Indomethacin Sensitive Headaches

Treatment options other than indomethacin for hemicrania continua and paroxysmal hemicrania are rare and second choice, but often necessary due to peptic ulcer. Although there are reports suggestive of a beneficiary use of COX 2 inhibitors [27], they should not be treatment of first choice [28] due to the associated adverse events. Treatment with topiramate, as well as lidocaine and methylprednisolone, has also been reported to be useful [28, 29]. However, recent developments of neurostimulation devices might offer a possibility to interact directly with the activated pathophysiological pathways of TACs. Data from a newly established animal model of TACs highlight the sphenopalatine ganglion (SPG) as a possible target for successful interaction [30••], though no data from human studies are available for hemicrania continua and paroxysmal hemicrania. The first results from a study of cluster headache patients with an on-demand stimulation of the SPG demonstrated it to be efficacious [31].

Pharmacology

As with many of the COX inhibitors, indomethacin has a bioavailability of about 98 %, plasma protein binding (albumin) is 90 %, and it is metabolized via the liver [32]. The half-life time lies between 3 and 10 h, maximal plasma concentrations are seen after 2 h [32, 33].

NSAIDs are known to cross the blood–brain barrier. Indomethacin shows the highest passage of the blood brain barrier when compared to naproxen and ibuprofen [34, 35], making a central action in headache treatment plausible [36••]. In the process of dissecting profiles of the different NSAIDs in regard to their action on COX 1 and/or COX 2, indomethacin was found in in vitro experiments to have a kinetic profile of time dependent tight binding, naproxen shows time dependent weak binding, and ibuprofen acts via competitive inhibition on COX 1 and COX 2 [37]. Further differentiation of indomethacin and other NSAIDs activities on COX 1 and COX 2 were made by analysis of the ratio of their ability in blocking either COX 1 or COX 2 [37–39]. The benzoyl group of the compound seems to be structurally relevant to indomethacin's COX 1 action, as it has been shown that replacement of this group by a 4-bromobenzy group results in a highly selective COX 2 inhibitor [40]. Inhibiting the synthesis of prostaglandins and inflammatory reactions, another mechanism has been found being suppressed in a dose dependent manner by indomethacin. Indomethacin suppressed phospholipase A2 in rabbit leukocytes [41]. This mechanism, however, seems not to be exclusive to indomethacin. Adding another mechanism to the inhibition of COX and phospholipase A2, the gluthation *S*-transferase (GST) is inhibited by indomethacin, as was shown in in-vitro assays [42•, 43, 44].

Headache Related Studies

Human Studies on the Effects of Indomethacin on Primary Headaches

The combination of indomethacin, prochlorperazine, and caffeine has been shown to have superior effects compared to nimesulide treatment of tension-type headache in a double blind randomized, parallel group, multicenter study of 54 patients [45]. Investigating the effect of intramuscular injected indomethacin (50 or 100 mg) in eight patients with chronic paroxysmal hemicrania (CPH) and twelve patients with hemicrania continua, it was found that for the CPH patients, the pain-free interval was increased by 50 mg indomethacin, and patients with hemicrania continua have a 13 h pain-free period [46]. In patients with CPH under indomethacin treatment, measurements of pain pressure thresholds were significantly reduced only on the affected side of the face, but not the asymptomatic side [47]. It was also suggested that this so-called "indotest" be used as a diagnostic tool. The "indotest" became a diagnostic tool used to verify the diagnosis of hemicrania continua and paroxysmal hemicrania. The doses recommended for the test are 100–200 mg intramuscular or oral [28, 48–50], and are higher than in the study of Antonaci et al. [46].

Animal Studies on the Effects of Indomethacin in Headache Models

Indomethacin and acetylsalicylic acid were shown to inhibit neurogenic plasma extravasation at the rat dura mater when they were given intraperitoneally prior to electrical stimulation of the trigeminal ganglion [51]; in higher concentrations, they also inhibited substance P-induced extravasation. It was hypothesised that these findings were caused by changes in vascular permeability and/or the smooth muscle contractility of dural vessels. The effect of the COX inhibitors indomethacin, acetylsalicylic acid, and naproxen was also seen when their effect on endothelin-1 induced vasoconstriction was investigated. Whilst low concentrations of these drugs enhanced the vasoconstriction induced by endothelin-1 in human artery, they had no such effect in porcine ophthalmic artery [52]. A clear effect on interleukin-β induced prostaglandin E synthesis via COX 2 in cultured rat trigeminal cells has been found. As a consequence of the blockage of prostaglandin-E release, the release of calcitonin gene-related peptide (CGRP) was inhibited [53]. Applying the model of intravital microscopy of the middle meningeal artery, an animal model for trigeminovascular activation with a high predictive value of potential anti-migraine effects of tested drugs [54, 55], Akerman et al. found indomethacin to be effective in inhibiting nitric oxide (NO) induced dural vasodilation [56]. In these experiments, however, indomethacin was not tested versus other drugs of the NSAID class. In another study, employing the same technique of intravital microscopy, it was demonstrated that indomethacin, but not naproxen or ibuprofen, had an effect on nitric oxide induced vasodilation [36••] when tested in doses resembling the ratio of doses used in headache therapy (animal doses: indomethacin 5 $mg kg^{-1}$, naproxen 30 $mg kg^{-1}$, ibuprofen 30 $mg kg^{-1}$). All of the tested drugs had a similar inhibitory effect on electrically induced meningeal vasodilation, mirroring an inhibitory effect of electrically induced release of CGRP from the trigeminal ganglion. A direct effect of indomethacin on CGRP or on the CGRP receptor is highly unlikely, as there was no effect seen when the dilatory effect of administered CGRP was tested in animals that were treated with indomethacin [36••]. The time course of onset of inhibition of electrically induced vasodilation showed an earlier onset for indomethacin than for ibuprofen. The effects on nitric oxide induced vasodilation are not caused by modification of any of the nitric oxide synthases, since the nitric oxide donor that was used in these experiments was a direct donor of NO (sodium nitroprusside) that does not require a nitric oxide synthase.

Nitric oxide induced effects in headache pathophysiology are of great interest, since it is known that application of NO-donors induces an acute headache, followed by a later

onset headache that concurs with migraine reported in patients [57]. Nitric oxide donors are therefore used as a tool for experimental human models of migraine [58, 59]. Nonetheless, NO can also be used to induce headaches that resemble the symptoms of cluster headache if the NO-donor glyceryltrinitrate (GTN) is given to cluster headache patient within an active cluster episode [60], and there is a case report of GTN-induced paroxysmal hemicranias [61]. Whilst the migraine-like and cluster-like headache developed with a delay, GTN-induced paroxysmal hemicrania started immediately after NO administration. This indicates that the NO induced migraine-like and cluster-like headaches require second messenger systems to be activated, whilst NO seems to have a more direct effect in paroxysmal hemicrania. In TACs, NO is known to play a role in the parasympathic loop [62]. The blood flow decrease through NO administration is independent from prostaglandins, but is at least in part induced by a NO induced release of CGRP [63]. In-vitro experiments demonstrate the ability of indomethacin in inhibiting NO production from rat microglia [64], a mechanism with potential headache protective effects within the trigeminonociceptive system. Recent studies also demonstrated a direct effect of indomethacin on trigeminal activation itself [30••, 65]. In the newly developed in-vivo model of TACs, Akerman et al. demonstrated an inhibitory effect of indomethacin on trigeminal nociceptive firing that was elicited by stimulation of the superior salivatory nucleus and recorded in the trigeminocervical complex. They also demonstrated the ability of indomethacin to inhibit the trigeminoautonomic activation in the tested animals [30••]. Indomethacin, oxygen, and sumatriptan were highly effective in this model, while naproxen and the CGRP-receptor antagonist olcegepant were less effective. Interestingly, indomethacin and naproxen demonstrated similar inhibitory effects on trigeminocervical firing in the trigeminocervical complex after dural electrical stimulation, but there is a significant difference for inhibitory effect on trigeminocervical firing after stimulation of the superior salivatory nucleus. Comparing indomethacin and naproxen, only indomethacin was able to inhibit blood flow changes measured in the rat lacrimal gland after stimulation of the superior salivatory nucleus as a model for activation of autonomic symptoms, demonstrating a direct effect on the craniovascular outflow [30••]. In another model, indomethacin, as well as ketorolac, has been shown to block central sensitization at the level of the trigeminocervical complex after application of an inflammatory soup on the rat dura mater. The increased firing rates of the neurons in response to tactile stimuli within the receptive field of the according neuron in the trigeminocervical complex were strongly inhibited by application of indomethacin 1 mgkg-1 intravenously, though this effect was only tested in three cells for indomethacin [65]. The combination of indomethacin, chlorperazine, and caffeine, indomethacin alone and sumatriptan were tested in a model of peripheral sensitization through injection of kainic acid intraperitoneally and in a model of central sensitization through intrathecal injection of NMDA. In these experiments, indomethacin alone or in combination was more potent in inhibiting the hyperalgesia tested with the hot plate test [66].

Non-Pain Related Research

New Findings—Potential Mechanisms Relevant to Indomethacin's Role in Headache Treatment

Recent research revealed potential anti-cancer and anti-dementia effects of NSAIDs that seem to be independent from their abilities in COX inhibition. Indomethacin demonstrated inhibition of cell growth, as well as induction of apoptosis in several tumor cell lines [67, 68]. Besides these direct effects of indomethacin, NSAIDs were shown to sensitize malignant glioma cells to the cytotoxicity of doxorubicin and vincristine, but not to the cytotoxic agents BCNU, VM26, camptothecin, cytarabine, or cisplatin [69]. A cell line of human uterine cervical cancer, however, did also show an increase of cytotoxicity of cisplatin if indomethacin was co-administered [70]. The effects were not mediated by the COX inhibition of the tested drugs (indomethacin and ibuprofen). In further experiments, the expression of the multidrug resistance protein was amenable by indomethacin, therefore making this mechanism highly likely to be relevant to the observed findings [69]. Hayeshi et al. discussed that the increased cytotoxicity of cisplatin, in cases when indomethacin is co-administered [70], might be solely due to inhibition of cisplatin export by multidrug resistance protein (MDRP), and not the effects of GST [43]. However, there is more evidence supporting a strong relationship linking GST and MDRP, therefore making it likely that the observed effects of indomethacin are caused by an interaction with the herein activated pathways [71]. Indeed, a study of the same group examined the interaction of GST and MRDP and their effect on NO storage and transport in cells. They demonstrated the involvement of GST in formation of complex-bound NO and the transport of these via MRDP to the interstitium [72••]. This demonstrates an important interaction of GST and MRDP in cytoprotection against the cytotoxicity of NO, possibly even having effects on the NO signaling between cells. The impact of this finding on pain relevant mechanisms remains unclear. Moreover, the results contrast with the inhibitory effect of indomethacin on NO activated mechanisms, as studied in the trigeminovascular model. These experiments suggest

that an inhibition of GST, as it is known to be induced by indomethacin, would lead to higher levels of unbound NO in the cell.

The formation of the amyloid β42 amino acid form of amyloid beta, which is being considered neurotoxic and a substantial component of the plaques found in patients suffering from Alzheimer's disease, was significantly decreased by indomethacin or ibuprofen, but not naproxen, in an in vivo setup. However, this result might only be a consequence of naproxen's comparatively poor ability to cross the blood brain barrier, and not due to a specific effect of the two other drugs [34]. In mounted hippocampal slices, indomethacin facilitated synaptic transmission, probably by stimulation of presynaptic glutamate release [73]. In the same study, the effect of indomethacin on learning and spatial memory was investigated and reported as being enhanced by indomethacin [73]. Two follow-up studies found that, in the rat hippocampal slices, α7 acetylcholine receptor responses were potentiated by activation of protein kinase C-ε [74, 75••], thereby demonstrating that the effects on memory function and learning found earlier are plausibly explained via these newly described and COX independent effects of indomethacin. However, not all of these effects are exclusive to indomethacin, and therefore might not be responsible for the observed effects in indomethacin sensitive headaches.

Observations of vasoconstriction after application of indomethacin led to further research concerning its neuroprotective value, in terms of lowering the intracranial pressure after severe head trauma or hepatic failure. Again, the effects are not seen with the other drugs of the NSAID class, and the implications of the decreased blood flow, as for example possible cerebral ischemia, are controversial. The human and animal research to date suggests, however, an altogether beneficial effect on the ICP and very importantly, on the cerebral perfusion, without clear evidence for cerebral microischemia [76]. The mechanisms responsible for the observed vasoconstriction remain unclear and theories linking this exclusively to the shift of an increased metabolism of arachidonic acid to vasoconstrictor substances (leukotrienes and products of the cytochrome p-450 enzyme), after blockade of the cyclooxygenase pathway cannot explain why only indomethacin shows this effect.

Conclusion

To date, the mechanism that is accountable for indomethacin's unique efficacy in the treatment of hemicrania continua and paroxysmal hemicrania has not been identified. Though it is possible that many mechanisms of NSAIDs other than COX inhibition are not exclusive to indomethacin, there are various lines of evidence supporting the existence of an exclusive effect. The overall effect of each of the NSAIDs is determined by many factors, such as pharmacokinetics, the ratio of interaction with the known mechanisms, and the mechanisms that are yet not fully understood. The value of the alteration of cerebral perfusion and the impact on the ICP through indomethacin application for headache therapy are unclear, and the mode of action at the level of the endothelium of vessels is not clear. However, animal models of headache have started to link the ability of indomethacin in modifying vasodilation to mechanisms other than COX dependent ones. [36••, 56]. The most recent data from the aforementioned research begin to link the effects of indomethacin seen on COX 1 and COX 2, GST, MDRP, and their effects on important cell signaling mechanisms, such as NO signaling. This might help to delineate indomethacin's ability to modify NO transmitted mechanisms in trigeminovascular activation [36••]. Animal data even highlight anatomical regions that are relevant and sensitive to indomethacin. The impact of indomethacin on neuronal signaling within the trigeminocervical systems remains to be further investigated; a general enhancement of neuronal signaling by indomethacin is somewhat contradictory to the inhibitory effects of indomethacin on meningeal evoked neuronal firing recorded in the trigeminocervical nucleus. Future headache research illuminating the role of GST in trigeminocervical signaling might be useful, as there is evidence that GST is involved in migraine pathophysiology [77]. The latter evidence is, however, still missing in models of trigeminovascular and trigeminocervical activation.

Conflict of Interest Dr. Oliver Summ declares that he has no conflict of interest.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. Eur J Neurol. 2009;16(9):968–81.
2. Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J. EFNS guideline on the treatment of tension-type headache—report of an EFNS task force. Eur J Neurol. 2010;17(11):1318–25.
3. May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol. 2006;13(10):1066–77.
4. Headache Classification Committee of the International Headache Society. The international classification of headache disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9–160.
5. • Evers S, Goadsby P, Jensen R, May A, Pascual J, Sixt G. Treatment of miscellaneous idiopathic headache disorders (Group 4 of the IHS classification)—report of an EFNS task force. Eur J

Neurol. 2011;18(6):803–12. *A review on therapeutic options of miscellaneous headaches that demonstrates the outstanding role of indomethacin as a treatment option in these headache entities*.
6. Martins IP, Parreira E, Costa I. Extratrigeminal ice-pick status. Headache. 1995;35(2):107–10.
7. Ammache Z, Graber M, Davis P. Idiopathic stabbing headache associated with monocular visual loss. Arch Neurol. 2000;57(5):745–6.
8. Mathew NT. Indomethacin responsive headache syndromes. Headache. 1981;21(4):147–50.
9. Raskin NH. The cough headache syndrome: treatment. Neurology. 1995;45(9):1784.
10. Mateo I, Pascual J. Coexistence of chronic paroxysmal hemicrania and benign cough headache. Headache. 1999;39(6):437–8.
11. Diamond S. Prolonged benign exertional headache: its clinical characteristics and response to indomethacin. Headache. 1982;22(3):96–8.
12. Dodick DW. Indomethacin-responsive headache syndromes. Curr Pain Headache Rep. 2004;8(1):19–26.
13. Frese A, Rahmann A, Gregor N, Biehl K, Husstedt IW, Evers S. Headache associated with sexual activity: prognosis and treatment options. Cephalalgia. 2007;27(11):1265–70.
14. Gelfand AA, Goadsby PJ. Primary sex headache in adolescents. Pediatrics. 2012;130(2):e439–41.
15. Guido M, Specchio LM. Successful treatment of hypnic headache with topiramate: a case report. Headache. 2006;46(7):1205–6.
16. Pinessi L, Rainero I, Cicolin A, Zibetti M, Gentile S, Mutani R. Hypnic headache syndrome: association of the attacks with REM sleep. Cephalalgia. 2003;23(2):150–4.
17. Prakash S, Dabhi AS. Relapsing remitting hypnic headache responsive to indomethacin in an adolescent: a case report. J Headache Pain. 2008;9(6):393–5.
18. Marziniak M, Voss J, Evers S. Hypnic headache successfully treated with botulinum toxin type A. Cephalalgia. 2007;27(9):1082–4.
19. Martins IP, Gouveia RG. Hypnic headache and travel across time zones: a case report. Cephalalgia. 2001;21(9):928–31.
20. Ghiotto N, Sances G, Di Lorenzo G, Trucco M, Loi M, Sandrini G, et al. Report of eight new cases of hypnic headache and mini-review of the literature. Funct Neurol. 2002;17(4):211–9.
21. Evers S, Rahmann A, Schwaag S, Ludemann P, Husstedt IW. Hypnic headache—the first German cases including polysomnography. Cephalalgia. 2003;23(1):20–3.
22. Seidel S, Zeitlhofer J, Wober C. First Austrian case of hypnic headache: serial polysomnography and blood pressure monitoring in treatment with indomethacin. Cephalalgia. 2008;28(10):1086–90.
23. Peters N, Lorenzl S, Fischereder J, Botzel K, Straube A. Hypnic headache: a case presentation including polysomnography. Cephalalgia. 2006;26(1):84–6.
24. Centonze V, D'Amico D, Usai S, Causarano V, Bassi A, Bussone G. First Italian case of hypnic headache, with literature review and discussion of nosology. Cephalalgia. 2001;21(1):71–4.
25. Lisotto C, Rossi P, Tassorelli C, Ferrante E, Nappi G. Focus on therapy of hypnic headache. J Headache Pain. 2010;11(4):349–54.
26. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. Brain. 1997;120(Pt 1):193–209.
27. Porta-Etessam J, Cuadrado M, Rodriguez-Gomez O, Garcia-Ptacek S, Valencia C. Are Cox-2 drugs the second line option in indomethacin responsive headaches? J Headache Pain. 2010;11(5):405–7.
28. Cittadini E, Goadsby PJ. Update on hemicrania continua. Curr Pain Headache Rep. 2011;15(1):51–6.
29. Morelli N, Mancuso M, Felisati G, Lozza P, Maccari A, Cafforio G, et al. Does sphenopalatine endoscopic ganglion block have an effect in paroxysmal hemicrania? A case report. Cephalalgia. 2010;30(3):365–7.
30. •• Akerman S, Holland PR, Summ O, Lasalandra MP, Goadsby PJ. A translational in vivo model of trigeminal autonomic cephalalgias: therapeutic characterization. Brain. 2012;135(Pt 12):3664–75. *This article highlights an effect of indomethacin that might arise from interaction with autonomic transmission at the level of the sphenopalatine ganglion and is possibly relevant to the treatment of trigeminoautonomic cephalalgias*.
31. Schoenen J, Jensen RH, Lanteri-Minet M, Lainez MJ, Gaul C, Goodman AM, Caparso A, May A. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study. *Cephalalgia* 2013, in press.
32. Helleberg L. Clinical pharmacokinetics of indomethacin. Clin Pharmacokinet. 1981;6(4):245–58.
33. Alvan G, Orme M, Bertilsson L, Ekstrand R, Palmer L. Pharmacokinetics of indomethacin. Clin Pharmacol Ther. 1975;18(3):364–73.
34. Eriksen JL, Sagi SA, Smith TE, Weggen S, Das P, McLendon DC, et al. NSAIDs and enantiomers of flurbiprofen target gamma-secretase and lower Abeta 42 in vivo. J Clin Invest. 2003;112(3):440–9.
35. Parepally JM, Mandula H, Smith QR. Brain uptake of nonsteroidal anti-inflammatory drugs: ibuprofen, flurbiprofen, and indomethacin. Pharm Res. 2006;23(5):873–81.
36. •• Summ O, Andreou AP, Akerman S, Goadsby PJ. A potential nitrergic mechanism of action for indomethacin, but not of other COX inhibitors: relevance to indomethacin-sensitive headaches. J Headache Pain. 2010;11(6):477–83. *This article identified an interaction of indomethacin with NO-mechanisms that was not shown by other drugs of the NSAID class. It implicates a possible importance to indomethacin's mechanism of action in indomethacin-sensitive headaches*.
37. Gierse JK, Koboldt CM, Walker MC, Seibert K, Isakson PC. Kinetic basis for selective inhibition of cyclo-oxygenases. Biochem J. 1999;339(Pt 3):607–14.
38. Noreen Y, Ringbom T, Perera P, Danielson H, Bohlin L. Development of a radiochemical cyclooxygenase-1 and -2 in vitro assay for identification of natural products as inhibitors of prostaglandin biosynthesis. J Nat Prod. 1998;61(1):2–7.
39. Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR. Selectivity of nonsteroidal antiinflammatory drugs as inhibitors of constitutive and inducible cyclooxygenase. Proc Natl Acad Sci U S A. 1993;90(24):11693–7.
40. Black WC, Bayly C, Belley M, Chan CC, Charleson S, Denis D, et al. From indomethacin to a selective COX-2 inhibitor: development of indolalkanoic acids as potent and selective cyclooxygenase-2 inhibitors. Bioorg Med Chem Lett. 1996;6(6):725–30.
41. Kaplan L, Weiss J, Elsbach P. Low concentrations of indomethacin inhibit phospholipase A2 of rabbit polymorphonuclear leukocytes. Proc Natl Acad Sci U S A. 1978;75(6):2955–8.
42. • Joachim A, Lautscham E, Christoffers J, Ruttkowski B. Oesophagostomum dentatum: effect of glutathione S-transferase (GST) inhibitors on GST activity and larval development. Exp Parasitol. 2011;127(4):762–7. *Indomethacins capabilities in gluthation S transferase inhibition were demonstrated*.
43. Hayeshi R, Chinyanga F, Chengedza S, Mukanganyama S. Inhibition of human glutathione transferases by multidrug resistance chemomodulators in vitro. J Enzyme Inhib Med Chem. 2006;21(5):581–7.
44. Vandenberghe Y, Ratanasavanh D, Glaise D, Guillouzo A. Influence of medium composition and culture conditions on glutathione S-transferase activity in adult rat hepatocytes during culture. In Vitro Cell Dev Biol. 1988;24(4):281–8.
45. Cerbo R, Centonze V, Grazioli I, Tavolato B, Trenti T, Uslenghi C, et al. Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine in the treatment of episodic tension-type headache: a double-blind, randomized, nimesulide-

controlled, parallel group, multicentre trial. Eur J Neurol. 2005;12(10):759–67.
46. Antonaci F, Pareja JA, Caminero AB, Sjaastad O. Chronic paroxysmal hemicrania and hemicrania continua. Parenteral indomethacin: the 'indotest'. Headache. 1998;38(2):122–8.
47. Antonaci F, Sandrini G, Danilov A, Sand T. Neurophysiological studies in chronic paroxysmal hemicrania and hemicrania continua. Headache. 1994;34(8):479–83.
48. Marmura MJ, Silberstein SD, Gupta M. Hemicrania continua: who responds to indomethacin? Cephalalgia. 2009;29(3):300–7.
49. Cittadini E, Goadsby PJ. Hemicrania continua: a clinical study of 39 patients with diagnostic implications. Brain. 2010;133(Pt 7):1973–86.
50. Cohen AS, Matharu MS, Goadsby PJ. Trigeminal autonomic cephalalgias: current and future treatments. Headache. 2007;47(6):969–80.
51. Buzzi MG, Sakas DE, Moskowitz MA. Indomethacin and acetylsalicylic acid block neurogenic plasma protein extravasation in rat dura mater. Eur J Pharmacol. 1989;165(2–3):251–8.
52. Bakken IJ, Vincent MB, White LR, Cappelen J, Skaanes KO, Sjaastad O. Low concentrations of lithium and cyclooxygenase inhibitors enhance endothelin-1 (ET-1)-induced contractions in human temporal artery, but not in porcine ophthalmic artery. Headache. 1992;32(10):475–9.
53. Neeb L, Hellen P, Boehnke C, Hoffmann J, Schuh-Hofer S, Dirnagl U, et al. IL-1beta stimulates COX-2 dependent PGE(2) synthesis and CGRP release in rat trigeminal ganglia cells. PLoS One. 2011;6(3):e17360.
54. Andreou AP, Summ O, Charbit AR, Romero-Reyes M, Goadsby PJ. Animal models of headache: from bedside to bench and back to bedside. Expert Rev Neurother. 2010;10(3):389–411.
55. Gupta S, Bhatt DK, Boni LJ, Olesen J. Improvement of the closed cranial window model in rats by intracarotid infusion of signalling molecules implicated in migraine. Cephalalgia. 2010;30(1):27–36.
56. Akerman S, Williamson DJ, Kaube H, Goadsby PJ. The effect of anti-migraine compounds on nitric oxide-induced dilation of dural meningeal vessels. Eur J Pharmacol. 2002;452(2):223–8.
57. Sances G, Tassorelli C, Pucci E, Ghiotto N, Sandrini G, Nappi G. Reliability of the nitroglycerin provocative test in the diagnosis of neurovascular headaches. Cephalalgia. 2004;24(2):110–9.
58. Iversen HK. Human migraine models. Cephalalgia. 2001;21(7):781–5.
59. Iversen HK, Olesen J. Headache induced by a nitric oxide donor (nitroglycerin) responds to sumatriptan. A human model for development of migraine drugs. Cephalalgia. 1996;16(6):412–8.
60. Ekbom K. Nitrolglycerin as a provocative agent in cluster headache. Arch Neurol. 1968;19(5):487–93.
61. Giffin NJ. Paroxysmal hemicrania triggered by GTN. Cephalalgia. 2007;27(8):953–4.
62. May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab. 1999;19(2):115–27.
63. Strecker T, Dux M, Messlinger K. Increase in meningeal blood flow by nitric oxide—interaction with calcitonin gene-related peptide receptor and prostaglandin synthesis inhibition. Cephalalgia. 2002;22(3):233–41.
64. Du ZY, Li XY. Inhibitory effects of indomethacin on interleukin-1 and nitric oxide production in rat microglia in vitro. Int J Immunopharmacol. 1999;21(3):219–25.
65. Jakubowski M, Levy D, Goor-Aryeh I, Collins B, Bajwa Z, Burstein R. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. Headache. 2005;45(7):850–61.
66. Ghelardini C, Galeotti N, Grazioli I, Uslenghi C. Indomethacin, alone and combined with prochlorperazine and caffeine, but not sumatriptan, abolishes peripheral and central sensitization in in vivo models of migraine. J Pain. 2004;5(8):413–9.
67. de Groot DJ, van der Deen M, Le TK, Regeling A, de Jong S, de Vries EG. Indomethacin induces apoptosis via a MRP1-dependent mechanism in doxorubicin-resistant small-cell lung cancer cells overexpressing MRP1. Br J Cancer. 2007;97(8):1077–83.
68. Pollard M, Luckert PH. Prolonged antitumor effect of indomethacin on autochthonous intestinal tumors in rats. J Natl Cancer Inst. 1983;70(6):1103–5.
69. Roller A, Bahr OR, Streffer J, Winter S, Heneka M, Deininger M, et al. Selective potentiation of drug cytotoxicity by NSAID in human glioma cells: The role of COX-1 and MRP. Biochem Bioph Res Co. 1999;259(3):600–5.
70. Ogino M, Minoura S. Indomethacin increases the cytotoxicity of cis-platinum and 5-fluorouracil in the human uterine cervical cancer cell lines SKG-2 and HKUS by increasing the intracellular uptake of the agents. Int J Clin Oncol. 2001;6(2):84–9.
71. Morrow CS, Smitherman PK, Diah SK, Schneider E, Townsend AJ. Coordinated action of glutathione S-transferases (GSTs) and multidrug resistance protein 1 (MRP1) in antineoplastic drug detoxification. Mechanism of GST A1-1- and MRP1-associated resistance to chlorambucil in MCF7 breast carcinoma cells. J Biol Chem. 1998;273(32).
72. •• Lok HC, Suryo Rahmanto Y, Hawkins CL, Kalinowski DS, Morrow CS, Townsend AJ, et al. Nitric oxide storage and transport in cells are mediated by glutathione S-transferase P1-1 and multidrug resistance protein 1 via dinitrosyl iron complexes. J Biol Chem. 2012;287(1):607–18. *This article highlights an interaction of indomethacin with nitric oxide mechanisms, demonstrating an effect of indomethacins on nitric oxide metabolism implicating high relevance to nitric oxide dependent mechanisms, including cell signaling*.
73. Kanno T, Yaguchi T, Nagata T, Shimizu T, Tanaka A, Nishizaki T. Indomethacin enhances learning and memory potential by interacting with CaMKII. J Cell Physiol. 2012;227(3):919–26.
74. Kanno T, Yaguchi T, Nagata T, Nishizaki T. Indomethacin activates protein kinase C and potentiates alpha7 ACh receptor responses. Cell Physiol Biochem. 2012;29(1–2):189–96.
75. •• Kanno T, Tsuchiya A, Shimizu T, Tanaka A, Nishizaki T. Novel indomethacin action: selective and direct activation of protein kinase C-epsilon. Cell Physiol Biochem. 2012;30(3):771–7. *Protein kinase C-epsilon has been shown being activated by indomethacin*.
76. Rasmussen M. Treatment of elevated intracranial pressure with indomethacin: friend or foe? Acta Anaesthesiol Scand. 2005;49(3):341–50.
77. Kusumi M, Ishizaki K, Kowa H, Adachi Y, Takeshima T, Sakai F, et al. Glutathione S-transferase polymorphisms: susceptibility to migraine without aura. Eur Neurol. 2003;49(4):218–22.