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Postoperative pain—from mechanisms to treatment

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Abstract

Introduction: Pain management after surgery continues to be suboptimal; there are several reasons including lack of translation of results from basic science studies and scientific clinical evidence into clinical praxis.

Objectives: This review presents and discusses basic science findings and scientific evidence generated within the last 2 decades in the field of acute postoperative pain.

Methods: In the first part of the review, we give an overview about studies that have investigated the pathophysiology of postoperative pain by using rodent models of incisional pain up to July 2016. The second focus of the review lies on treatment recommendations based on guidelines and clinical evidence, eg, by using the fourth edition of the "Acute Pain Management: Scientific Evidence" of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine.

Results: Preclinical studies in rodent models characterized responses of primary afferent nociceptors and dorsal horn neurons as one neural basis for pain behavior including resting pain, hyperalgesia, movement-evoked pain or anxiety- and depression-like behaviors after surgery. Furthermore, the role of certain receptors, mediators, and neurotransmitters involved in peripheral and central sensitization after incision were identified; many of these are very specific, relate to some modalities only, and are unique for incisional pain. Future treatment should focus on these targets to develop therapeutic agents that are effective for the treatment of postoperative pain as well as have few side effects. Furthermore, basic science findings translate well into results from clinical studies. Scientific evidence is able to point towards useful (and less useful) elements of multimodal analgesia able to reduce opioid consumption, improve pain management, and enhance recovery.

Conclusion: Understanding basic mechanisms of postoperative pain to identify effective treatment strategies may improve patients' outcome after surgery.

Keywords: Postoperative pain, Surgical incision, Sensitization, Multimodal analgesia, Ketamine, Pregabalin

1. Introduction

More than 230 million people undergo surgery each year worldwide and the number is increasing annually.[183] Surgery causes commonly postoperative pain that should be alleviated as soon and as effective as possible to reduce suffering, to promote the healing process and rehabilitation and to prevent complications. However, clinical pain management after surgery is far from being successful despite dramatically increased scientific evidence in this area. Many patients suffer from severe pain after surgery[55,104]; even less well recognized, many develop chronic pain after surgery which might be, at least in part, a result of undertreated acute postoperative pain.[50] One reason for this undertreatment is the limited translation of basic and clinical scientific findings into clinical practice. For example, pain after surgery is a very specific entity; it is neither the result of an inflammatory process alone nor only the result of isolated injury to nerves. Although inflammation and neural tissue damage occur, the pathophysiology of postoperative pain is unique and the consequences are specific. However, treatment strategies used in the "real world" are still not based on these findings. Furthermore, analgesics and techniques with limited adverse effects and/or with benefits targeting specific aspects of postoperative pain (eg, movement-evoked pain) are lacking. It is necessary to gain new insights into the mechanisms of postoperative pain in experimental and clinical settings to develop therapeutic options with greater efficacy and less risk of adverse effects than those available today. Finally, comprehensive evidence based on results from clinical studies enhances knowledge, but needs to be implemented

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into clinical practice as well. Here we will present and discuss results from basic science studies and clinical scientific evidence generated within the last 2 decades to improve knowledge and enable translation of these findings into clinical practice more rapidly.

2. Animal-experimental basic research

2.1. Animal models of postoperative pain: an overview

To identify the mechanisms inherent in incision-induced postoperative pain, a specific surgery-related animal model in rats was developed in the 90s of the last century.[19,197] By using this plantar incision model (and other animal models developed thereafter investigating specific aspects of pain after surgical trauma), we have learnt much about the underlying neurophysiology of incisional pain (comprehensive reviews are found here).[18,20,141,189]: In general, it ensued that many of those mechanisms inherent in pure inflammatory, antigen-induced or neuropathic pain are not relevant for incisional pain and vice versa. In the following, we will summarize some aspects of incisional pain, which were identified by using the plantar incision model. Because of the high number of published studies during the last 2 to 3 decades (PubMed entry key words: "Incision" and "animals" and "postoperative pain" revealed 397 hits, November 9, 2016), we are not able to report all findings. Those up to 2007 are mainly summarized in the reviews quoted here.[20,141] We will provide a selective overview of topics, which are relevant to the pain field in general and specifically interesting to those dealing with postoperative pain in the clinical setting.

2.1.1. Brief description of the models

The original plantar incision model was developed in 1996 by Brennan et al.[19] Briefly, under general anesthesia, a 1-cm longitudinal incision is performed through the glabrous skin, fascia, and plantar muscle of the rat hind paw. The skin is surgically sutured, then the animals recover from anesthesia; pain behavior can be measured from one hour thereafter. The combination of transsection of the skin, fascia, and retracted muscle compares well to the tissue trauma of patients undergoing surgery.[18] Similar to patients after surgery, rats develop short-lasting nonevoked guarding pain behavior (for a short time period of approximately 2 days after incision) and longer lasting evoked pain-related behavior to punctate mechanical stimuli (von Frey hairs); these pain behaviors are seen as a surrogate for nonevoked resting pain (lasting some days) and evoked pain (lasting several days till weeks) after surgery, respectively, and are therefore relevant to postoperative pain in patients.[35,166]

Mechanical hyperalgesia occurs at the side of the incision (primary hyperalgesia) and in an area surrounding the injury (secondary hyperalgesia) for several days after the incision.[196] Furthermore, heat hyperalgesia, but not cold hyperalgesia,[156] is prominent at the site of the incision lasting up to approximately 7 days.[196] Secondary heat hyperalgesia (usually measured as withdrawal thresholds to radiant heat) does not occur after this incision. Additionally, an incision model within the hairy skin hind paw of rats was developed for better investigation of secondary mechanical hyperalgesia in animals (gastrocnemius incision).[134]

More recently, anxiety- and depression-like behaviors were investigated after plantar incision; for example, rats show an increase in anxiety-like avoidance behaviors in the light/dark box and an increase in depression-like behavior (sucrose preference test) for some days after incision.[86,168] Other studies assessing anxiety-like behavior after incision in rats gave similar results by using slightly different approaches and study designs.[36,97] Interestingly, the anxiety-like behavior lasted longer than hyperalgesia in 2 (but not one) of these studies. As anxiety and other psychological factors such as depression, catastrophizing, and stress enhance acute and promote long-lasting pain after surgery, investigation of appropriate assays in animals might be relevant.

In 2003, the rat plantar incision model has been transferred from the rat to the mouse with some modification (5 mm incision, one mattress suture, modulated assessment of mechanical, and heat hyperalgesia), with very similar results in behavioral experiments.[136] To investigate prolonged pain after a surgical incision more specifically, a skin and muscle retraction injury model (SMIR) was introduced.[48] Here, a 1.5 to 2-cm incision is made in the skin of the medial inner thigh, 4 mm medial to the saphenous vein. The superficial (gracilis) muscle layer is then incised (7–10 mm) approximately 4 mm medial to the saphenous nerve and retracted with a microdissecting retractor for one hour. The tissue is sutured with silk. Mechanical hyperalgesia in the SMIR model lasts for up to 3 weeks and therefore much longer than after plantar incision, but heat hyperalgesia was not observed. Interestingly, the SMIR model has been transferred to a porcine model of prolonged incisional pain,[28] which may have some very interesting advantages: For instance, pigs have a greater phylogenetic proximity with humans like a similar metabolism and a comparable skin anatomy with great homology in wound healing compared to rodents.[33] These advantages could be deployed for validating new topical and localized treatment options for postoperative, incisional pain in human. Many other pain models related to surgical and trauma injuries have been developed and a comprehensive overview can be found in the review quoted here.[189] One interesting model, for instance, is the back hairy skin incision model that represents another clinically relevant model for pain behavior after an incision in hairy skin.[43,125] However, because of space limitations and because of the fact that the plantar (and more recently the SMIR incision) is used most frequently for studying mechanisms of incisional pain, we will mainly focus on these 2 models. Finally, an incision model in humans is also available and may provide an important link between animal studies and patients (eg, see [23,47,77,139]). However, we will mainly focus on results from animal studies for this review.

2.2. Mechanisms of pain caused by a surgical incision

The patterns of pain behavior after surgical incisions in rodents indicate that peripheral and central sensitization occur. In neurophysiological experiments, activation and sensitization of peripheral nociceptors[62,133] and spinal dorsal horn neurons[196] were identified, and their specific mechanisms were investigated further.

2.2.1. Spinal sensitization after surgical incision

It is very intriguing that spinal administration of many substances that are able to prevent central sensitization in other pain models failed to produce a significant effect after incision; the first studies in the plantar incision model indicated this using spinal *N*-methyl-D-aspartate (NMDA) receptor antagonists which basically failed to produce any effect.[49,137,196] These effects (or rather failure of effects) led to the assumption that an incision causes a different "form" of spinal sensitization compared to other pain entities. Additional pharmacological support for a unique spinal

sensitization process after incision came from pharmacological studies showing that non-NMDA/α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor antagonists are involved in the spinal transmission of pain behavior after incision.[195,198,199] This again differs from many other pain models and was somehow striking by firstly questioning the general "rule" of a NMDA receptor-dependent central sensitization process relevant for certain types of pain, eg, after an incision and secondly "promoting" another rather new player in the game, namely the non-NMDA receptor group. The first issue was elaborated further by studies investigating the role of preemptive analgesia for postoperative pain, where NMDA receptors had earlier been identified as key molecules.[140] Spinal sensitization after the plantar incision is maintained (at least initially) by the afferent barrage of sensitized nociceptors[133] and the non-NMDA/AMPA receptor group is maintaining this process which is responsible for nonevoked pain and hyperalgesia after incision.[198] More recent studies further elucidated mechanisms of AMPA-receptor mediated pain and hyperalgesia after incision and found that phosphorylation of the AMPA receptor GluR1 subunit at Serine-831 via phospho kinase C gamma (PKCγ), but not other conventional PKC's isoforms (PKCα, βI and βII), leads to an increased trafficking of Ca^{2+} permeable AMPA receptors in the neuronal plasma membrane and might play a role for incisional pain.[181] Interestingly, AMPA receptor phosphorylation was enhanced under (social defeat) stress after incision[96]; at the same time, incision-induced punctate mechanical hyperalgesia was prolonged. Besides phosphorylation of AMPA receptors, one subunit, GluR1, but not GluR2, is upregulated in the spinal cord ipsilateral to an incision. The regulation of the surface delivery of this spinal AMPA receptor subunit is caused by stargazin (member of the AMPA receptor regulatory protein family), and selective down-regulation of stargazin was able to reduce synaptic targeting of GluR1 subunit and nonevoked pain behavior and mechanical hyperalgesia caused by plantar incision[60] (**Fig. 1**). These spinal AMPA receptor subunits and the mechanisms regulating them after incision are therefore useful targets for drugs to treat pain after surgery in the future. However, spinal NMDA-receptor blockade might still have some indications. For example, remifentanil-induced enhanced mechanical hyperalgesia after incision in rats is regulated via phosphorylation of spinal NR2B at Tyr1472 which was prevented by ketamine.[59] This has clinical implications as discussed below.

Studies showing different effects of spinal substances on different pain modalities are very interesting. Two examples are an effect on mechanical hyperalgesia, but not on nonevoked guarding pain and vice versa; and the activation of spinal aminobutyric acid (GABA)-receptors, especially $GABA_A$ and $GABA_B$, attenuated the generation of mechanical/heat hyperalgesia but not nonevoked pain after plantar incision.[143] Similarly, the selective inhibition of spinal pERK1/2 before incision exclusively altered mechanical hyperalgesia after incision but not nonevoked pain.[160,177] A comparable differentiation has been shown by Reichl et al.[145]; the inhibition of glutamate transporter (GluT) upregulation via mitogen-activated protein kinase p38 enhanced acute nonevoked pain after plantar incision, but did not alter mechanical or heat hyperalgesia. Interestingly, the effect of GluT inhibition extended the acute phase and lasted for approximately 2 weeks after incision. Thus, development of prolonged pain after surgery may be a result of impaired GLuT upregulation via p38 indicating a role spinal GluT in the prevention of chronic pain after incision. In the same way, prolonged pain behavior after the plantar incision was reported by inhibition of spinal cannabinoid receptors (CB_1 and CB_2) and dysregulation of mitogen-activated protein kinase phosphatase-3.[3,152] Mitogen-activated protein kinase phosphatase-3 knockout mice showed a persistent mechanical hyperalgesia up to 21 days after surgical incision; this correlated with persistent phosphorylation of spinal p38 and extracellular signal-regulated kinases (ERKs)-1/2 in neurons and microglia on postoperative day 12.

Together, these studies indicate the relevance of assessing the effect of various compounds after plantar incision in different pain behavior assays (nonevoked pain behavior, mechanical hyperalgesia), in particular to determine potential clinical relevance (resting pain vs movement evoked pain) after surgery.[35,166] Secondly, these studies identify factors relevant for prolongation of incisional pain; this may translate to mechanisms relevant for the development of chronic pain after surgery, another important clinical issue.[39,80]

Many other studies were undertaken to investigate pharmacological options to influence pain and hyperalgesia after incision by spinal modulation. Because of space limitations, we refer to **Table 1** and to a review of studies published earlier than 2007.[141]

However, we assess here some studies investigating the role of multimodal analgesia for postoperative pain, highly relevant to clinical practice. For example, subcutaneous co-administration of morphine and gabapentin generates a dose-dependent antihyperalgesic synergistic effect.[132] Similarly, intrathecal administration of gabapentin together with diclofenac, in doses not affecting nociception, reduced secondary hyperalgesia after incision. Thus, diclofenac augments the antihyperalgesic effects of gabapentin through spinal action.[120] These findings highlight that certain combinations of medicines might offer benefits in the treatment of postsurgical pain and need to be assessed in future clinical studies.

2.2.2. Peripheral sensitization after incision

After plantar incision, peripheral C- and Aδ-fibers are sensitized contributing to nonevoked pain and heat and mechanical hyperalgesia in the early days after incision.[8,62,133] Some of the underlying mechanisms were investigated within the last 10 years. Combined behavioral and neurophysiological experiments revealed that muscle nociceptors play a central role in the genesis of nonevoked guarding behavior after incision; the mechanism seems to be the spontaneous activity of C-fibers sensitized after incision.[18,187,188] In contrast, a skin incision without a muscle tissue injury seems to be responsible for inducing mechanical hyperalgesia after incision; muscle injury seems to be not required.[18,187,188] A series of studies revealed mechanisms inherent in (muscle) fiber sensitization after incision. They basically found a decrease in pH (pH ~6.8) and an increase in lactate concentration (6 mM) that correlated well with a peak in pain behaviors at 1 to 2 days after incision.[83,184] Similarly, a decrease of oxygen tension in both skeletal muscle and skin was detected immediately after incision for several days[74]; together with an increased lactate and decrease pH (see above), these ischemic-like conditions in the incisional wound are likely to contribute to peripheral sensitization (eg, muscle C-fibers, see[81]) and pain behavior (eg, nonevoked pain) after incision.[74] Furthermore, a response of muscle C-fibers to antagonists to acid-sensing ion channels (ASICs) in cultured dorsal root ganglion (DRG) neurons points towards the role of tissue acidity in nonevoked pain behavior after incision.[81] Interestingly, the ASIC3 channel is upregulated early after incision in muscle tissue innervating DRG neurons and seems to be important for nonevoked incisional pain, weight-bearing, and also partially for heat hyperalgesia. The role of ASIC3 for heat hyperalgesia is being controversially

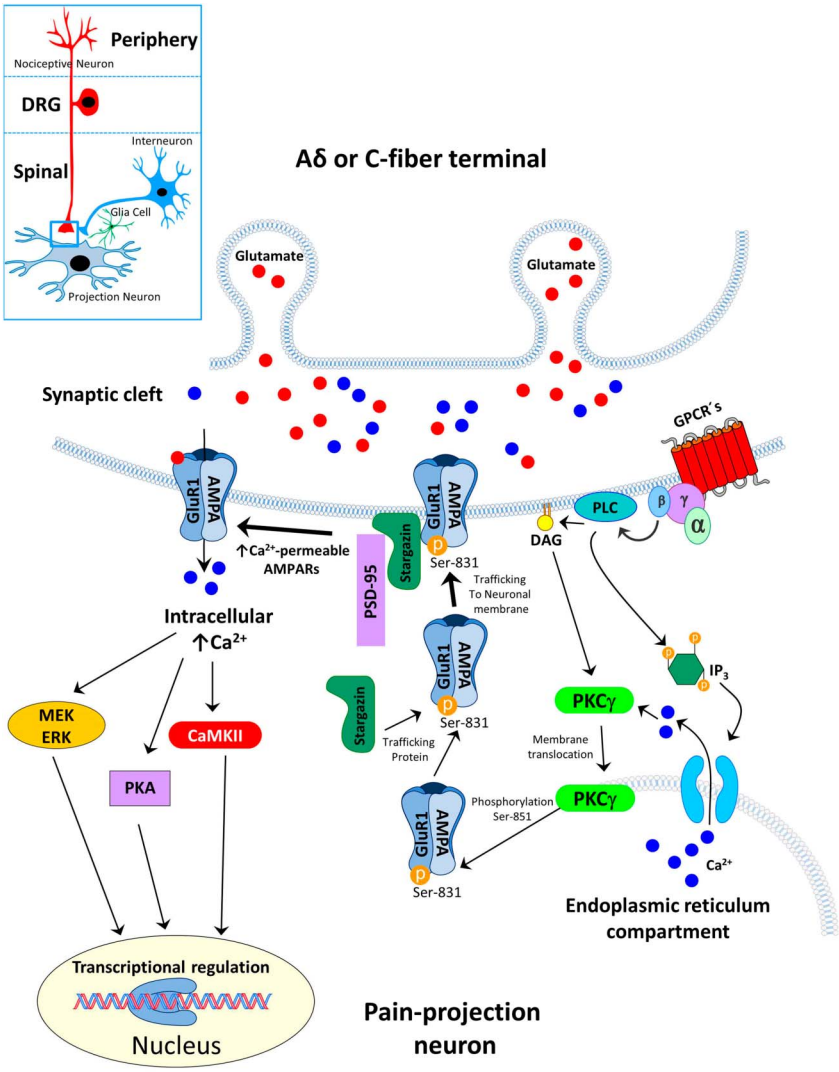

Figure 1. Postoperative pain is associated with increased trafficking of the GluR1 subunit of AMPA-receptors by phosphorylation of Ser-831. Surgical plantar incision enhances the membrane translocation of PKCγ, but not other PKC isoforms, and induces the phosphorylation the Ser-831 site of the GluR1 subunit from AMPA-receptors. Stargazin interacts with the phosphorylated subunit in the endoplasmic reticulum compartment and trafficking into the neuronal membrane.[60,181] The enhanced phosphorylation of GluR1 subunit and interaction of stargazin increased insertion of Ca^{2+} -permeable AMAPA receptors in the postsynaptic density (via PSD-95) that enhanced spinal nociceptive transmission. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Ca, calcium; CaMKII, Ca^{2+}/calmodulin-dependent protein; DAG, diacylglycerin kinase II; ERK, extracellular-signal Regulated Kinase; GluR, AMPA receptor subunit; GPCR´s, G-Protein-coupled recetors; IP_3, inosit-1,4,5-trisphosphat; MEK, mitogen-activated protein kinase kinase; P, phosphat; PKA, phospho kinase A; PKCγphospho kinase C gamma; PLC, phospholipase C; PSD-95, postsynaptic density-95; Ser, serine.

discussed in the literature with regard to different pain models. Whereas in vivo knockdown or specific inhibition via toxin APETx2a leads to complete remission of heat hyperalgesia after Complete Freund's Adjuvant (CFA) injection,[41] mechanical but not heat hyperalgesia after carrageenan injection into the muscle seems to be ASIC3 mediated.[161] Together, the role of ASIC (eg, ASIC3) channel blocker for pain in general and specifically for incisional pain needs further investigation.

The role of specific peripheral mechanisms contributing to hyperalgesia after the incision has been investigated as well. There are 2 important aspects, which will be highlighted here: Firstly there are different nociceptors that seem to be responsible for heat vs mechanical hyperalgesia after incision. Secondly, the molecular mechanisms of the fiber sensitization process responsible for mechanical and heat hyperalgesia after incision differ in many ways to other pain entities. Hints for the first aspect came from early studies using pretreatment of the incision site with a low dose of capsaicin (transient receptor potential vanilloid 1 receptor agonist); this reduced the heat hyperalgesia (and nonevoked pain) but not mechanical hyperalgesia after incision.[61] Consistent with other pain models, there is an upregulation of peripheral (and spinal) transient receptor potential vanilloid 1, which contributes to the development of heat (but not mechanical) hyperalgesia after incision.[10,138,174] There are many other examples differentiating mechanical and heat hyperalgesia after incision, which we will not address in detail but which are represented in **Table 1**.

One example for the second aspect, a differential sensitization process relevant for hyperalgesia after incision compared to inflammation or neuropathic pain, is the important role of calcitonin gene-related peptide in inflammation-related pain (CFA), which is not involved in spontaneous pain or mechanical

Table 1

Pharmacological modulation of incision-induced pain behavior.

Targets	Incision type	Species	Altered expression	Substance	Pain behavior	Literature
Voltage/Ligand-gated ion channels						
α2δ subunit voltage-gated Ca^{2+} channels	Plantar incision	Rat		Gabapentin (s.c.) preincision, S-(+)-3-Isobutylgaba (s.c.) preincision	↓ Mechanical/heat hyperalgesia	46
				Gabapentin (i.t.)	↓ Mechanical hyperalgesia	32
				Gabapentin (p.o.) intracerebroventricular	↓ Mechanical hyperalgesia	63
				Gabapentin (s.c) + Morphine (s.c)	↓ Mechanical hyperalgesia	132
	SMIR	Rat		Gabapentin (i.p.) post-SMIR	↓ Mechanical hyperalgesia	49
N-type voltage-sensitive Ca^{2+} channels	Plantar incision	Mice		Armed spider peptide Tx3-5 (i.t.) preincision/postincision	↓ Mechanical hyperalgesia	128
ASIC3	Plantar incision	Rat	↑ 4 h, DRG	siRNA (i.t.), APETx2 or PcTx1 (i.pl.)	↓ Nonevoked pain, heat hyperalgesia, weight bearing	40
NMDA-receptor	Plantar incision	Rat		MK-801 (NMDA-Antagonist) (i.t.) postincision AP5 (NMDA-Antagonist) (i.t.) postincision	↔ Mechanical hyperalgesia, ↔ nonevoked pain	195
	Plantar incision	Rat		Ro 25-6981 (NR2B antagonist) (i.t.) preincision	↓ Mechanical/thermal hyperalgesia 2 h after incision	70
	Gastroemicus incision	Rat		MK-801 (NMDA-Antagonist) (i.t.) postincision	↓ Secondary mechanical hyperalgesia ↑ motor impairment	135
	SMIR	Rat		MK-801 (i.p.) post-SMIR	↔ Mechanical hyperalgesia	49
AMPA/Kaniat (KA)	Gastroemicus incision	Rat		NBQX (AMPA/KA-Antagonist) (i.t.) JSTX (Ca2+ permeable AMAP/KA Antagonist)	↓ Secondary mechanical hyperalgesia	135
	Plantar incision	Mice		NBQX (AMPA/KA-Antagonist) (i.t.)	↓ Mechanical/heat hyperalgesia	198
$5\text{-}HT_3$	Plantar incision	Mice		Ondansetron ($5\text{-}HT_3$ antagonist) (i.pl.)	↓ Mechanical hyperalgesia	126
P2X	Plantar incision	Rat		TNF-ATP (P2X purinoceptor antagonist) postincision (i.pl.)	↓ Heat hyperalgesia	51
P2X7R	SMIR	Rat	↑ 1–22d, spinal	BBG (P2X7R-antagonist) (i.t.) A438079 (P2X7R-antagonist) (i.t.) Preincision, once daily for 7 d	↓ Mechanical hyperalgesia	193
$GABA_A$	Plantar incision	Rat	↔, spinal	Muscimol IT	↓ Mechanical/heat hyperalgesia, ↔ nonevoked pain	143
TRPV1	Plantar incision	Rat		Capsaicin (i.pl), preincision	↓ Heat hyperalgesia/nonevoked pain, ↔ mechanical hyperalgesia	61
	Plantar incision	Rat		SB366791 (TRPV1 receptor antagonist) (i.t., 15 min preincision; i.pl., 30 min preincision)	↓ Heat hyperalgesia, ↔ mechanical hyperalgesia	174
	Plantar incision	Rat		SB366791 postincision (i.pl.)	↓ Heat hyperalgesia	51
	Plantar incision	Mice		$TRPV1^{-/-}$ KO	↓ Heat hyperalgesia, ↔ mechanical hyperalgesia	10,138
TRPA1	Plantar incision	Rat		Chembridge-5861528 (TRPA1 antagonist) (i.pl.), 15 min preincision)	↓ Mechanical hyperalgesia/nonevoked pain	182
Neurotransmitter-transporter						
GLAST (glutamate transporter, GT)	Plantar incision	Rat	↑ 2 h–14 d, spinal	DL-TOBA (GT-inhibitor) (i.t.) postincision	↑ Long lasting nonevoked pain; ↔ mechanical/heat hyperalgesia	144
GLT-1 (glutamate transporter, GT)	Plantar incision	Rat	↑ 24 h, spinal	DL-TOBA (GT-inhibitor) (i.t.) postincision	↑ Long lasting nonevoked pain; ↔ mechanical/heat hyperalgesia	
G protein-coupled receptors/channels						
5-HT (serotonin)$_{2A}$	Plantar incision	Mice		Ketanserin ($5\text{-}HT_{2A}$ antagonist) (i.pl.)	↓ Mechanical hyperalgesia	126
		Rat		TCB-2 ($5\text{-}HT_{2A}$-Agonist) (i.t.) Ketanserin ($5\text{-}HT_{2A}$-Antagonist) (i.t.)	↑ Mechanical hyperalgesia; ↓ mechanical hyperalgesia	42
H_1 (histamine)	Plantar incision	Mice		Promethazine (H_1 antagonist) (i.pl.)	↓ Mechanical hyperalgesia	126
$GABA_B$	Plantar incision	Rat	↔, spinal	Baclofen (i.t.)	↓ Mechanical/heat hyperalgesia, ↔ nonevoked pain	143

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Table 1 (*continued*)

Pharmacological modulation of incision-induced pain behavior.

Targets	Incision type	Species	Altered expression	Substance	Pain behavior	Literature
Somatostatin receptor type 2 (sstr2)	Plantar incision	Rat	↑ 8 h, ↓ 1 d, spinal	Somatostatin (i.p.) postincision thrice daily	↓ Mechanical hyperalgesia, ↔ heat hyperalgesia	142
μ-opioid receptor (MOR)	SMIR	Rat		Morphine (i.p.) post-SMIR	↓ Mechanical hyperalgesia	49
	Plantar incision	Rat		Morphine (i.p.) postincision Buprenorphine (i.p.) postincision	↓ Mechanical hyperalgesia/nonevoked pain	73
	Plantar incision	Rat		Tramadol (i.pl./i.v) postincision	↓ Mechanical hyperalgesia	162
	Plantar incision	Mice	↔, DRG	Remifentanil (MOR-agonist) (s.c.) postincision	↑ Mechanical/heat hyperalgesia	25
CB (cannabinoid receptor) type 1/2	Plantar incision	Rat		AM281 (CB1 antagonist) and AM630 (CB2 antagonist) (i.p.) postincision (twice daily until POD9)	↑ Mechanical hyperalgesia (up to 15 d)	3
	Plantar incision	Rat		JWH015 (CB2 agonist) (i.t.) postincision	↓ Mechanical hyperalgesia	149
Imidazoline-2 (I_2)	Plantar incision	Rat		CR4056 (I_2 receptor ligand) (p.o.) postincision	↓ Mechanical hyperalgesia	88
α_{2B}-adrenoceptor	Plantar incision	Rat		Centhaquin citrate (α2A/B-adrenoceptor-agonist) (i.p.) postincision	↓ Mechanical/heat hyperalgesia ↓ nonevoked pain	94
Toll-like receptors (TLRs)						
TLR4	SMIR	Rat	↑ 5–20 d; DRG	LPS-RS (TLR4 inhibitor) preincision and daily 10 d post (i.t.)	↓ Mechanical hyperalgesia	31
Neurotrophic factors/peptides/mediators						
BDNF (brain-derived neurotrophic factor)	Plantar incision	Rat	↑ 24 h, spinal			107
NGF (nerve growth factor)	Plantar incision	Rat	↑ 4 h–10 d, skin ↑ 4 h, 48 h muscle			164
			↑ 4 h–5 d, skin	anti-NGF antibody (i.p.) preincision	↓ Heat hyperalgesia/nonevoked pain, ↔ mechanical hyperalgesia	9
Bradykinin	Plantar incision	Rat		des-Arg8, Leu8-bradykinin (dALBK) i.v.; HOE-140 (bradykinin B_2 receptor antagonist) i.v.	↔ Mechanical/heat hyperalgesia	95
				HOE-140 postincision (i.pl.) [des-Arg^{10}]-HOE 140 postincision (i.pl.)	↓ Heat hyperalgesia	51
CGRP	Plantar incision	Mice	↔ 4 and 24 h	αCGRP KO mice	↔ Mechanical/heat hyperalgesia, ↔ nonevoked pain, ↔ paw thickness	67
C5a (complement component C5)	Plantar incision	Mice	↑ 4 h–3 d, skin ↔ spinal/DRG	PMX53 (C5a receptor antagonist) (i.pl.) preincision	↓ Mechanical/heat hyperalgesia ↓ paw thickness	69
Endothelin-1	Plantar incision	Rat		Endothelin-1 (potent vasoconstrictor) (i.t.)	↓ Mechanical hyperalgesia	30,115
Neuropeptide Y	Plantar incision	Rat	↓ 1, 2 d, muscle	NPY (i.t.)	↓ Mechanical/heat hyperalgesia ↓ nonevoked pain	190
NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells)	Plantar incision	Rat	↑ 2 h–3 d, spinal	Pyrrolidinedithiocarbamate (PDTC) (i.t.) preincision	↓ Mechanical/heat hyperalgesia	191
Cytokines						
TNF (Tumor necrosis factor) α	SMIR	Rat	↑ 5–20 d, spinal	Thalidomide (TNF-α synthesis inhibitor) (i.p.) 30 min prior SMIR, for 10 d	↓ Mechanical hyperalgesia	171
	SMIR	Rat	↑ 1–22 d, spinal			193
IL (interleukin)-1β	Plantar incision	Mice	↑ 2–72 h, hind paw plantar skin	Anakinra (i.pl.)	↓ Mechanical/heat hyperalgesia	153
	Plantar incision	Mice		IL-1αβ KO Mice	↔ Mechanical hyperalgesia	65
	Plantar incision	Mice	↑ 2–48 h, hind paw plantar skin			98
	Plantar incision	Rat	↑ 1–48 h, skin ↑ 1, 4 h muscle			164
	SMIR	Rat	↑ 5–20 d; DRG	IL-1ra (IL-1 receptor antagonist) preincision and daily 10 d post (i.t.)	↓ Mechanical hyperalgesia	31
IL-6	Plantar incision	Rat	↑ 4, 48 h, skin ↑ 1 h–10 d muscle			164
IL-10	Plantar incision	Rat	↑ 4, 48 h, skin ↑ 4 h–10 d muscle			
TLR4	SMIR	Rat	↑ 5–20 d; DRG	LPS-RS (TLR4 inhibitor) preincision and daily 10 d post (i.t.)	↓ Mechanical hyperalgesia	31

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Table 1 (*continued*)

Pharmacological modulation of incision-induced pain behavior.

Targets	Incision type	Species	Altered expression	Substance	Pain behavior	Literature
LIF (leukemia inhibitory factor)	Plantar incision	Rat	↑ 1 d, skin ↑ 2, 5 d, muscle	Anti LIF antibody (i.pl.) preincision	↔ mechanical/heat hyperalgesia ↔ nonevoked pain	165
Enzymes						
Tryptase	Plantar incision	Mice		Gabexate (Tryptase-Inhibitor) preincision (i.pl.); ENMD-1068 (PAR-2 antagonist) preincision (i.pl.)	↓ Mechanical hyperalgesia, ↓ nonevoked pain	127
Caspase 1	Plantar incision	Mice	↑ 2–72 h, hind paw plantar skin	Ac-YVAD-CMK (caspase-1 inhibitor) (i.pl.) VRTXSD727	↓ Mechanical/heat hyperalgesia, ↓ paw thickness, ↓ hind paw temperature	98
iNOS	Plantar incision	Rat	↑ 4 h, spinal	N-(3-(Aminomethyl)benzyl)acetamidine (1400 W, iNOS-inhibitor) preincision/postincision (i.t./i.pl.)	Preincision/postincision (i.t./i.pl): ↓ mechanical/ heat hyperalgesia, ↓ nonevoked pain	53
NOS	Plantar incision	Rat		L-NOARG (NO synthase inhibitor) postincision (i.pl.)	↓ Heat hyperalgesia	51
p38	Plantar incision	Rat		SB203580 (p38MAPK-inhibitor) Postincision daily for 3 d (every 12 h, i.t.)	↑ Long lasting nonevoked pain; ↔ mechanical/ heat hyperalgesia	144
p38	Plantar incision	Mice	↑ 5–12 d, spinal	—	—	152
p-p38	SMIR	Rat	↑ 5–20 d; DRG	SB203580 (p38MAPK-inhibitor) pre-SMIR and daily 10 d post (i.t.)	↓ Mechanical secondary hyperalgesia	31
			↑ 3–11 d; spinal	SB203580 (i.t.) postincision	↓ Mechanical secondary hyperalgesia	66
MEK (pERK1/2)	Plantar incision	Rat	↑ 4 h, spinal	PD98059 (i.t.) preincision	↓ Mechanical hyperalgesia; ↔ heat hyperalgesia and nonevoked pain	177
Mitogen-activated protein kinase phosphatase (MKP)-3	Plantar incision	Mice	↑ 5–12 d, spinal	MKP-3$^{-/-}$ KO Mice	↑ Mechanical hyperalgesia up to 21 d, ↑ paw thickness up to 7 d in MKP-3 KO mice	152
				SB239063 and PD98059 (i.t.)	↓ Mechanical hyperalgesia on day 12 in MKP-3 KO mice	
PI (phosphatidylinositol) 3- kinase	Plantar incision	Mice	↑ 2 and 6 h, spinal	Wortmannin; LY294002 (i.t., i.p.) preincision	↓ Mechanical/heat hyperalgesia and nonevoked pain, ↓ c-Fos positive cells	186
COX (Cylcooxygenase) 2	Plantar incision	Rat	↑ 4 h, 1–3 d, skin	SC-236 (COX-2 inhibitor) (s.c.) preincision	↓ Heat hyperalgesia	26
MAO (monoamine oxidase)-B	Plantar incision	Mice		Selegiline (MAO-B-inhibitor) (p.o.) preincision	↓ Mechanical hyperalgesia	178
Epigenetic Mechanism						
DNA metyltransferase	Plantar incision	Mice		5-AZA-CdR (DNA methyltransferase inhibitor) (i.p.) preincision	↓ Mechanical/heat hyperalgesia ↓ paw edema	170
Histon deacetylase (HDAC)	Plantar incision	Mice		SAHA (Suberoylanilide hydroxamic acid, HDAC-inhibitor) (i.p.) preincision (1 d and 2 h), postincision (daily for 4 d)	↑ Mechanical hyperalgesia ↔ heat hyperalgesia	169
Histon-acetyltransferase (HAT)	Plantar incision	Mice		Anacardic acid (ACA, HAT-inhibitor) (i.p.) preincision (1 d and 2 h), postincision (daily for 4 d)	↓ Mechanical hyperalgesia ↔ heat hyperalgesia	
Cells						
Neutrophil granulocyte	Plantar incision	Mice		Anti-Ly6G/Gr-1 Antibody (i.p) preincision	↑ Heat hyperalgesia 24 h, ↓ paw edema	153
Mast cell	Plantar incision	Mice		Compound 48/80 (i.pl.) preincision Cromoglycate (i.pl.) preincision Ketotifen (p.o.) preincision	↓ Mechanical hyperalgesia, ↓ nonevoked pain	126,127,192
Microglia	Plantar incision	Rat	↑ 1–4 d, spinal			150
	SMIR	Rat	↑ 3–12 d, spinal			193
Astrocytes	Plantar incision	Rat	↑ 1–4 d, spinal			150
	SMIR	Rat	↑ 3–12 d			193

↑, increased; ↓, decreased; ↔, no alteration; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionate; ASIC, acid-sensing ion channels; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; ERK, extracellular signal-regulated kinase; i.p., intra peritoneal; i.pl., intra plantar; i.t, intrathecal; i.v., intravenous; KO, knockout; NMDA, *N*-methyl-D-aspartate; p.o., per oral; POD, postoperative day; s.c., subcutaneous; SMIR, skin/muscle incision and retraction; TRPV1, transient receptor potential vanilloid 1.

and heat hyperalgesia after incision in mice.[67] Further confirmation for an unique peripheral sensitization process after incision came from a study investigating 84 mRNAs from the neurotrophins and inflammatory cytokines families in skin, muscle, and DRG after plantar incision.[164] As demonstrated, most alterations in the mRNA expression are present in incised skin and muscle, less in the DRG. They occur within the first 48 hours after incision when the mechanical and heat hyperalgesia, as well as guarding pain, is most obvious. In particular, genes for wound healing, reinnervation, and the immune response are differently expressed in comparison to other pain models.[164] More examples supporting this are shown in **Table 1**.

Only recently peripheral inflammatory cell responses were investigated after incision injury in animals. For instance, migration of neutrophilic granulocytes (NGs) into tissue traumatized by incision occurs shortly after surgery, reaching a maximum at 24 hours and declining rapidly to baseline within 3 days.[27,45,153] Neutrophilic granulocytess release many well-known proinflammatory mediators and contain endogenous opioid peptides (met-enkephalin and β-endorphin).[146] Sahbaie and colleagues demonstrated that the systemic depletion of NGs (with Gr-1 antibody) reduced the paw edema and the interleukin-1β (IL-1β) concentration, but increased significantly the heat hyperalgesia for 24 hours and did not alter the mechanical hyperalgesia after plantar incision in mice.[153] This suggests a role of endogenous opioids (released by NGs) for incisional pain similar to that shown in inflammatory pain models.[147] However, another study from Carreira et al.[27] used the same method to deplete NGs but showed attenuation of mechanical hyperalgesia after incision; they suggested the role of CXCL-1-CXCR1/2 recruitment of NGs after incision. Presumably, proinflammatory mediators from NGs (IL-1β and C5a) may play a role for hyperalgesia after incision.[69,99,153] Thus, as the local concentration of C5a after the incision is increased, this complement factor may provide a novel target for analgesic drug development.[69,99] However, the exact role of NGs in postoperative pain is currently unclear because of the contradictory results of both NG-depletion studies.[27,153]

The prevention of mast cell degranulation (mast cell membrane stabilization with Cromoglycate) or depletion of mast cell mediators (with Compound 48/80 prior to incision), thus inhibiting the effect of histamine, 5-HT, and tryptase (a serine protease localized exclusively in mast cells) reduce the mechanical hyperalgesia and nonevoked pain in mice.[127,192] Similar effects are observed by administration of tryptase-binding receptor antagonist (protease-activated receptor 2, PAR2).[127] These results suggest a role of mast cells contributing to hypersensitization after incision. However, it should be noted that the mast cell degranulation alone seems insufficient to promote pain (eg, allergies, some drug administration).

2.2.3. Neuroplastic changes in the brain after incision

Our understanding of the processing of pain in the human brain has improved significantly[105]; however, activity and neuroplasticity in the pain matrix after incision contributing to pain-related behavior remains poorly understood. A recent study in animals indicates directly how the brain reacts to an incision compared to inflammation by using functional magnetic resonance imaging to assess oxygenation levels of the blood as an indirect measure of neural activity and functional magnetic resonance spectroscopy.[5] Mechanical stimulation of the incised hind paw showed blood oxygen level dependent (BOLD) signals, which differed significantly in quantity and quality to BOLD signals related to mechanical stimulation of the hind paw after CFA inflammation. Similarly, BOLD signals after electrical stimulation in both animal models differed to mechanical stimulation.[5] However, GABA levels (measured with functional magnetic resonance spectroscopy) increased in both pain models within the thalamus, during rest and during mechanical stimulation.[5] Thus, the thalamus might play a central role for hyperalgesia regardless of the pain entity and GABA neurotransmission might be involved. Further imaging studies investigated central neuroplastic changes relevant for the development of more chronic pain after incision. Human functional magnetic resonance imaging studies confirmed the role the thalamus[139] and indicated a lack of descending inhibition in enhanced pain responses of patients with chronic pain after incision.[22,23] By using the positron emission tomography-method, Romero et al.[148] demonstrated long-lasting changes in glucose metabolism in central pain-related areas and opioid-related pathways up to 21 days after incision. The metabolic changes in the pain matrix were positively correlated with hypersensitivity caused by naloxone injection in rats which received remifentanil anesthesia earlier.[148] This suggests long-lasting neuroplastic adaptations in central opioid circuits possibly contributing to chronic pain after incision.

Systemic administration of gabapentin, or inhibition of ERK within the anterior cingulate cortex (ACC) early after surgery, but not systemic morphine, reduced incision-induced anxiety.[36,86,97] Interestingly, ERK-inhibition reduced anxiety-like behavior and mechanical hyperalgesia early after surgery (1 hour), but (different to inflammatory and neuropathic pain) in the later phase (6 hour), it exclusively reduced anxiety.

A recent study showed that presurgical or postsurgical exposure to stress factors like immobilization and force swimming test does not change the basal pain perception to different stimuli, such as mechanical, hot and cold, but prolongs the duration of incision-induced hyperalgesia after incision.[26] By blocking spinal glucocorticoid receptors or removing the adrenal glands, stress-induced prolongation of incision-induced hyperalgesia was abrogated. These results indicate a direct connection between the activation of the hypothalamic-pituitary-adrenal axis through presurgery and postsurgery stress and duration of incision-induced hypersensitivities. Maternal adversity in the form of perinatal stress and depression may also activate the hypothalamic-pituitary-adrenal system and increased incisional pain in adult rats.[85] Thus, acute stress might be—similar to other psychological factors—relevant for the transformation of acute into chronic pain after surgery.[26]

2.3. Epigenetic modulation after incision

In recent years, a growing body of publications has examined the potential of the epigenetic modulation, such as DNA methylation, histone acetylation and noncoding RNA, for chronic pain conditions.[90,131] Some epigenetic results are now available for acute postoperative incisional pain in animals.[154,169,170] An incision seems to induce changes in global DNA methylation, which leads to increased incision-induced hyperalgesia. Peripheral and spinal inhibition of a DNA methyltransferase via 5-Aza-2′-deoxycytidine led to attenuation of the mechanical and heat hyperalgesia and reduced hind paw swelling.[170] Furthermore, epigenetic modulation of spinal *Bdnf*− (brain-derived neurotropic factor) and *Pdyn*− (prodynorphin) genes via acetylated Histone H3K9 in mice under chronic opioid exposure seems to be involved in opioid tolerance after incision.[154] Notably, different histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid or trichostatin A, attenuated heat hyperalgesia[7] or

mechanical hyperalgesia[159] in an inflammatory (CFA) and in a neuropathic pain model, but exacerbated mechanical hyperalgesia after incision in mice.[169] Taken together, these first epigenetic results suggest that peripheral and spinal epigenetic modulation are involved in increased postoperative nociceptive sensitization (**Fig. 2**). The additional influence of epigenetic regulation by drugs (eg, opioids) or environmental input could induce long-lasting changes in the pain system, one possible cause for a transformation from acute to chronic conditions.

2.4. New drugs in the pipeline

In recent years, nonclassical active pharmaceutical ingredients from venoms of spiders[128,163] or from other sources[66,82,84,100,106,122,155,180,200,201] have been tested for their potential to reduce mechanical/heat hyperalgesia and/or non-evoked pain or gait abnormalities after incision. Some substances act directly at receptors, such as the vitexin, a C-glycosylated flavone present in several medicinal herbs, which binds to $GABA_A$ and opioid receptors.[200] Some more recent studies report that curcumin (diferuloylmethane), a phenolic constituent of turmeric, reduces incisional inflammation, nociceptive hypersensitivity,[201] spontaneous pain, and functional gait abnormalities by increasing the level of TGF-β in incisional skin.[155] Other substances block spinal N-type voltage-sensitive Ca^{2+} channels and reduce mechanical hyperalgesia after incision without altering the normal nociceptive sensitivity, eg, venom of the Brazilian armed spider *Phoneutria nigriventer*.[128] These nonclassical active pharmaceutical substances have characteristics making them suitable as potential candidates for the development of new analgesics for postoperative pain.

2.5. Challenges in the translation of animal studies to man

The translation of findings from animals to patients (and back) is one of the greatest challenges in modern (pain) research. Previous studies have shown that the direct translation of results from rodent experiments is difficult and should be performed and interpreted with caution.[111] One major disadvantage of many animal pain models is that they are not representing the pain etiology or pain entity they are translated to.[111,112] The development of more sophisticated animal models, mimicking human pain conditions to improve bench-to-bedside translation, is part of the current discussion.[24,34,111] The same, in fact, relates to human experimental pain models and their translation to patients and needs attention as well.[103] Furthermore, the portfolio of behavioral pain measurements in animals does not represent well clinically relevant pain aspects in humans. For several years, we and others assess spontaneous pain behavior in rats after incision representative of pain at rest in patients.[19,133,143,144] Hyperalgesia to pinprick stimuli are assessed in rats frequently; interestingly, the same stimuli are used to assess hyperalgesia around a surgical wound in patients,[37,167] the mechanisms behind this might be relevant for central sensitization and prolongation of pain after surgery and are therefore useful to study.[44,93] More recently, movement-evoked pain and pain-related anxiety and depression are explored in animals after incision; presumably, these might be other translatable

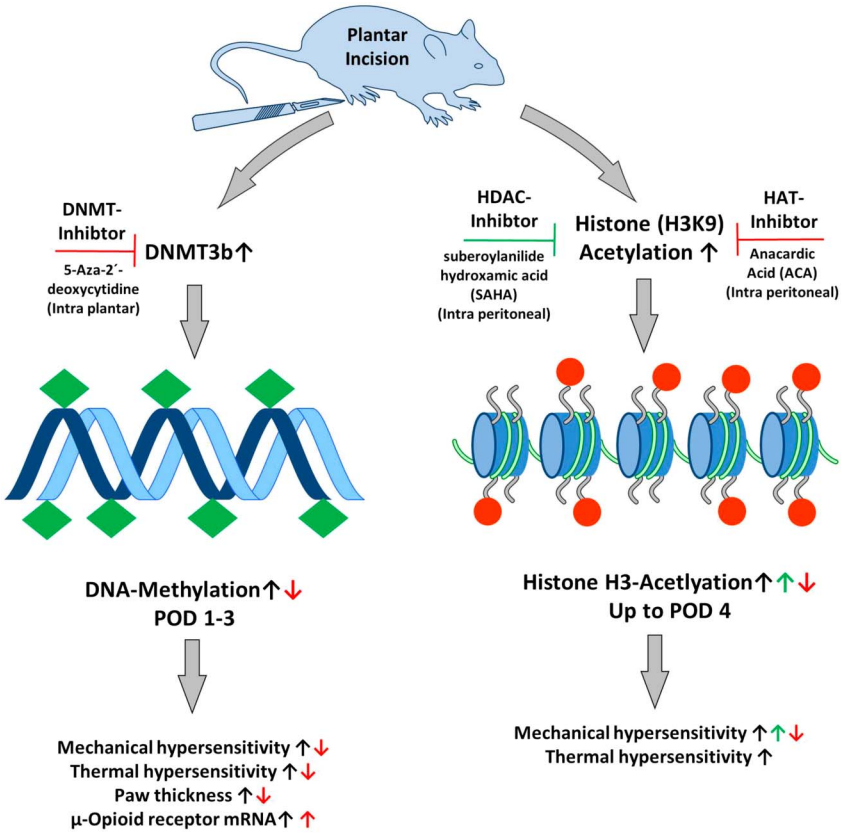

Figure 2. Epigenetic mechanisms modulate nociceptive sensitization after incision. Intra plantar (i.pl.) application of DNA-methyltransferase (DNMT) inhibitor (5-Aza-2′-deoxycytindine) reduced DNA-methylation and attenuated mechanical/heat hyperalgesia (↓), paw thickness (↓), and reinforced peripheral μ-opioid receptor mRNA expression (↑).[170] The inhibition of Histon-deacetylase (HDAC) with suberoylanilide hydroxamic acid (SAHA, i.p.) reinforced mechanical hyperalgesia (↑). However, treatment of histon acetyltransferase inhibitor anacardic acid (ACA, i.p.) attenuated mechanical hyperalgesia (↓).[169]

pain-related behaviors and should be focused on in the future.[111,112,176] Together, adequate animal pain models (eg, incisions for surgical pain,[18,19]) and relevant pain behavior assessed in these models combined with experimental human studies[139] will pave the way for a refined and more applicable bench-to-bedside translation in postoperative pain.

3. Evidence for clinical management of postoperative pain

The preceding part of this article has outlined quite clearly that postoperative pain as a manifestation of acute pain is markedly more complex than originally thought. The complexity of postoperative pain requires, therefore, considerably more than simply applying opioids as required. It is, therefore, not surprising that there is now a large scientific evidence basis for the management of postoperative pain. This has been summarized recently in the fourth edition of the document "Acute Pain Management: Scientific Evidence", published by the Australian and New Zealand College of Anaesthetists and its Faculty of Pain Medicine.[157] The sheer size of this document reflects the complexity quite well; the document has nearly 650 pages, assesses over 8500 references, and condenses the evidence-based information in 669 key messages. It is obvious that it would be impossible to summarize that entire document in this article. The article will, therefore, concentrate on overarching key strategies and specific treatment options as far as they are of more general importance.

3.1. Multimodal analgesia

The concept of multimodal ("balanced") analgesia has been introduced into the management of postoperative pain more than 20 years now.[79] The concept suggests that it is superior to combine analgesics with different modes or sites of action, as such combinations will improve analgesia, reduce opioid requirements (so-called "opioid-sparing" effect), and thereby reduce the adverse effects of opioids.[194] This concept is in line with the observations in basic science models that combinations of, for example, peripherally and centrally acting analgesic compounds are of value here. In addition, such multimodal approaches show further benefits with regard to other postoperative outcomes. Just to mention a few examples here, after total knee joint replacement, multimodal analgesia increases patient satisfaction scores and permits earlier achievement of milestones of physical therapy.[87] Similarly, after spinal surgery, use of multimodal analgesia improves postoperative mobilization.[108] In view of data showing that increased opioid use, with resulting opioid adverse effects (in particular nausea, vomiting, and constipation), delays recovery after surgery and thereby leads to extended hospital stay with increased costs,[124] multimodal analgesia would reduce such complications, speed up recovery, and possibly even reduce hospital costs. This is nicely reflected in the fact that more or less all approaches using enhanced recovery after surgery protocols include multimodal analgesia concepts as one component.[78] However, it has to be acknowledged that multimodal analgesia by itself does not result in early rehabilitation or enhanced recovery after surgery. To achieve these goals, multimodal analgesia needs to be integrated into a holistic and multidisciplinary approach to the postoperative period.[119] In particular, again the importance seems to be the opioid-sparing effect, as avoidance of oral opioids in the postoperative period after colorectal surgery reduces the length of stay.[2] This is confirmed by other data that show that opioid-sparing analgesic techniques reduce postoperative ileus.[11]

In this context, it is interesting to look in more detail at which compounds are actually useful components of multimodal analgesia and should thereby be combined with opioids.

3.2. Reduction of peripheral sensitisation due to inflammation

3.2.1. Nonsteroidal anti-inflammatory drugs

As outlined before, peripheral sensitisation of nociceptors leading to primary hyperalgesia is an important contributor to postoperative pain. It is, therefore, not surprising that in clinical reality drugs which are reducing peripheral prostaglandin concentration and thereby leading to reduced peripheral sensitisation are a useful component of multimodal analgesia. In randomized controlled trials[52] and their meta-analyses, these drugs fulfill all 3 requirements on multimodal analgesia, ie, improved analgesia, reduced opioid requirements, and reduced adverse effects of opioids.[109] A reduction of postoperative nausea and vomiting, one of the most disturbing adverse effects of opioids in the early postoperative period, is reported. COX-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs) (coxibs) have similar efficacy to nonselective NSAIDs.[113] However, they are superior in the postoperative setting because of reduced adverse events.

With regard to bleeding complications, coxibs lack platelet inhibition[116] and therefore cause less postoperative blood loss than nonselective NSAIDs[64] and are comparable to placebo.[101] Furthermore, these compounds show a gastric ulceration rate similar to placebo and significantly lower than nonselective NSAIDs in high-risk patients, even for short-term use.[56] Coxibs do not cause bronchospasm in patients with NSAID-exacerbated respiratory disease, a complication, which can occur with nonselective NSAIDs.[114] Concerns about cardiovascular complications of coxibs, identified with rofecoxib and leading to its withdrawal,[21] have not eventuated with short-term use of parecoxib[158] or even long-term use of celecoxib.[123]

The effect of NSAIDs may be enhanced by the addition of paracetamol as the combination of paracetamol and NSAIDs is more effective than either compound alone.[129]

3.2.2. Corticosteroids

Dexamethasone as an anti-inflammatory corticosteroid is widely used in anesthetic practice to prevent nausea and vomiting.[38] Other effects include an improvement of the quality of recovery and reduced fatigue.[117] In addition, dexamethasone in therapeutic doses reduces postoperative pain scores and opioid consumption.[179] However, these effects are small and only statistically significant and might not be of clinical relevance. In addition, there is still an ongoing debate about potential risks of perioperative steroid administration with regard to induction of hyperglycemia, increasing risk of infection and bleeding and possibly malignancy recurrence.[173] A large randomized controlled trial currently underway will try to address these unresolved questions (https://www.paddi.org.au).

3.3. Reduction of secondary hyperalgesia due to central sensitisation

As outlined in detail in the preceding part of the article, it is obvious that central sensitisation plays a much more relevant role in the development of postoperative pain than previously thought.

Findings in this setting illustrate that contrary to common beliefs, central sensitisation can occur within a very short time span and can significantly contribute to the overall picture of a postoperative pain state. It is therefore not surprising that there is increasing interest in the use of medications, which are attenuating such states of secondary hyperalgesia due to central sensitisation. A number of these compounds have become components of clinically useful multimodal analgesia. These include the NMDA receptor ketamine, the alpha-2-delta ligands pregabalin and gabapentin and the alpha-2-adrenergic agonist's clonidine and dexmedetomidine.

3.3.1. Ketamine

Ketamine is a noncompetitive antagonist of the NMDA receptor when used in subanaesthetic doses. Meta-analyses support the use of perioperative IV infusions of low-dose ketamine (in the range of around 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$) with resulting improved analgesia, an opioid-sparing effect and reduction of opioid side effects such as postoperative nausea and vomiting.[89] The benefits of ketamine are, in particular, seen in patients after major surgeries that are suffering severe pain (VAS >7/10). This explains why these benefits have been shown after thoracic and upper abdominal and major orthopedic surgery. In addition, not only in laboratory settings but also in the clinical settings, NMDA receptor antagonists such as ketamine are reducing the development of opioid-induced hyperalgesia, for example after remifentanil use.[185] It is, therefore, not surprising that ketamine is also a useful analgesic in the settings of patients with established opioid tolerance[13,175] and preoperative high opioid use.[102] Similar findings with regard to opioid-sparing and improvement of analgesia have also been found with a perioperative infusion of magnesium which has to be regarded as another NMDA-receptor antagonist.[118] Last, not least, there are data supporting the effect of perioperative ketamine in reducing the incidence of chronic postsurgical pain (see preventive analgesia).[29]

3.3.2. Alpha-2-delta ligands

The alpha-2-delta ligands pregabalin and gabapentin, which were developed for the treatment of neuropathic pain where they find their most relevant indication, have also been shown to have an effect on central sensitisation and are, therefore, for example, indicated in the treatment of fibromyalgia with FDA approval. In this context, it is, therefore, not surprising that for both compounds there is evidence from meta-analyses supporting their role as a component of multimodal analgesia.[110,172] Data show reduced pain scores as well as reduced opioid consumption and thereby reduced adverse effects of opioids. This beneficial effect can be achieved with a single preoperative dose. In addition, the anxiolytic effect of these drugs should be taken into consideration and might be an additional beneficial factor,[130] again in analogy to the basic science findings.

3.3.3. Alpha-2-adrenergic agonists

Perioperative systemic use of alpha-2 agonists such as clonidine and dexmedetomidine also fulfills the criteria for successful multimodal analgesia resulting in reduced pain intensity, opioid consumption, and nausea.[15] However, with their use, potential adverse effects such as hypotension and bradycardia and possibly dose-dependent sedation need to be considered.

In conclusion, the concept of multimodal analgesia is supported by a large clinical data set, which shows that addressing both peripheral and central sensitisation after surgical incision leads to improved analgesia with reduced opioid requirements and thereby opioid side effects. Current data do not permit a decision on which combinations of how many components may comprise multimodal analgesia after what kind of surgical incision. However, from a practical point of view it seems to become increasingly routine in the setting of acute pain services to use an NSAID (best seems to be a COX-2 selective one) routinely, paracetamol and (eg, before major procedures, in healthy patients) an alpha-2-delta ligand as standard components of multimodal analgesia with rescue opioid being available on top of this. Other components such as ketamine and alpha-2 agonists are used in specific indications. The role of corticosteroids is not yet fully established in this setting and requires further investigation.

3.4. Procedure-specific postoperative pain management

The basic science data presented above suggest that depending on the type and location of the incisional model, different pain states result. Again this is confirmed by clinical data which show that analgesics may have different efficacies in different surgical settings.[57] This is true even for a simple analgesic like paracetamol, which is significantly less effective after orthopedic surgery (relative risk reduction 1.87) than after dental extraction (relative risk reduction 3.77). Current large meta-analyses used to calculate the number needed to treat of analgesic agents might pool data from different postoperative pain states and thereby ignore the specific effects of a specific analgesic in a specific postoperative pain state.[57] In addition, it has to be acknowledged that different surgical procedures do not only cause different pain states but also pain states of different severities in different locations. These observations and the support by basic science have led to the development of the concept of procedure-specific postoperative pain management. Treatment pathways for the management of postoperative pain after different surgical procedures can be developed in an evidence-based fashion by analyzing the literature specific to the respective procedure.[72] Guidelines for a number of surgical procedures of different types have been developed by the PROSPECT initiative with the consideration of primarily procedure-specific evidence (www.postoppain.org). The guidelines can be found at the website of this initiative, and most of the guidelines have been accompanied by publications in the peer-reviewed literature with regard to these specific procedures.

3.5. Acute postoperative neuropathic pain

Neuropathic pain is still widely considered a chronic pain state. However, clinical experience and clinical data, as well as the animal data provided above, are showing that neuropathic pain can occur acutely and can be a component of postoperative pain. The literature shows that for example following sternotomy 50% of patients presented with dysaesthesia in the early postoperative period as a manifestation of acute neuropathic pain.[4] As in other chronic neuropathic pain states, a manifestation of neuropathic pain is accompanied by increased pain severity. Similarly, after cancer surgery, use of a screening tool in a prospective setting found acute neuropathic pain in the first week postoperatively in around 10% of the cases.[68] A case series in a general surgical population identified an incidence in the range of 3% to 4%.[151] It is, therefore, relevant for clinicians looking after postoperative

patients (and even more so after post-traumatic patients) to identify a neuropathic pain component, which might then require appropriate treatment, for example, with alpha-2-delta ligands or ketamine on top of commonly used opioids.

3.6. Preventive analgesia

Nerve injury leading to acute neuropathic pain is one of the major risk factors for the progression of acute to chronic pain.[1] Chronic postsurgical pain is much more common than usually thought and the estimated incidence of chronic severe pain with an intensity of more than 5/10 occurs in 2% to 10% of patients after surgery.[157] Besides nerve injury as a risk factor, other risk factors include preexisting preoperative pain, preoperative anxiety, catastrophizing as well as genetic predisposition. Postoperative factors are again severe acute postoperative pain and psychosocial risk factors similar to those in the preoperative setting. This is in line with some of the observations with regard to behavioral changes observed in animal studies. In view of nerve injury as a risk factor, it is not surprising that a large percentage of chronic postsurgical pain has features of neuropathic pain.[71]

With regard to the prevention of such pain states, there has been a significant change in concepts away from the previously supported pre-emptive analgesia approach to a preventive analgesia approach.[91] Pre-emptive analgesia is defined as a preoperative treatment, which is more effective than the identical treatment administered after the incision. The key difference is the timing of the administration. It has become increasingly obvious that preventive analgesia, ie, an analgesic effect beyond its expected duration is a more useful approach. For practical terms, this has been defined as analgesia which persists beyond 5.5 half-lives of a medicine.[76] In the context of prevention of chronic surgical pain, it is also important to maximize the benefits of any analgesic strategy by continuing the treatment into the postoperative period as long as the sensitising stimulus persists. With regard to the preventive effect on chronic postsurgical pain, best data are available for the use of regional or neuraxial analgesia. A meta-analysis supports the use of epidural analgesia after thoracotomy and the use of paravertebral blocks after breast cancer surgery.[6] Data at lower levels of evidence support the use of spinal anesthesia over general anesthesia for Caesarean section[121] and hysterectomy,[17] as well as the use of epidural analgesia after major abdominal surgery[92] and for amputations with regard to the reduction of phantom limb pain.[54] Interesting specifically for phantom limb pain is the idea of decreasing the already existing preoperative pain to reduce phantom limb pain after surgery; here, both epidural analgesia and systemic opioids seem to be effective.[75] Other data support the use of perioperative local anesthetics for wound infiltration.[14,16] However, it is important in this context to realize that intravenous lignocaine also has preventive effects on acute postoperative pain[12] and in one small study reduced chronic postsurgical pain.[58]

Further evidence supports the use of ketamine as a preventive treatment for chronic postsurgical pain. A meta-analysis of 14 rather small randomized controlled trials shows a reduction of chronic postsurgical pain at 3 and 6 months, in particular if ketamine is administered for more than 24 hours perioperatively.[29] With regard to the alpha-2-delta ligands gabapentin and pregabalin, there may be an effect on preventing chronic postsurgical pain; however, the data are currently rather contradictory and looking at only a few usually small studies with a large degree of heterogeneity so that uncertainty continues here.[29,33]

In conclusion, the current evidence base for the management of acute postoperative pain is significant. Much of the clinical data, which support certain approaches are in line with findings in the experimental setting. However, there are a number of discrepancies here and it will be interesting to see if the development of new compounds based on basic science studies will further help to improve the management of acute postoperative pain. It remains important to realize that postoperative pain management is not only a humanitarian task to reduce patient suffering and improve patient satisfaction but that treatment of acute postoperative pain has the potential to reduce morbidity possibly even mortality after surgery and in parallel enhance recovery, improve rehabilitation, reduce hospital stay and thereby overall hospital cost.

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