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Developmental neurobiology as a guide for pharmacological management of pain in neonates

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A B S T R A C T

Pain in newborn children should be prevented due to negative short- and long-term consequences. A good understanding of the development of the nociceptive system in newborns is necessary to enable optimal pain assessment, and most importantly to treat and prevent pain adequately in neonates. So far, preclinical juvenile animal studies have led to a tremendous amount of information regarding the development of the nociceptive system. In addition, they have made clear that the developmental stage of the nociceptive system may influence the mechanism of action of different classes of analgesics. Age specific analgesic therapy, based on post-menstrual age, should therefore be considered by incorporating information on the developmental stages of the nociceptive system in combination with knowledge from pharmacokinetic and –dynamic studies in neonates.

1. Introduction

The International Association for the Study of Pain (IASP) has defined 'pain' as '*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*' with the note that '*Pain is always subjective and each individual learns the application of the word pain through experiences related to injury in early life*' [1]. Since pain is subjective, self-report is the golden standard. However, newborns and young children are generally considered unable to express their pain verbally and cannot quantify their pain by self-report. Therefore, other techniques, like parent reports or validated behavioural pain scales used by trained nurses, are needed to optimally assess pain in newborns [2,3].

A good understanding of the development of the nociceptive system in newborns is necessary to improve pain assessment and most importantly in order to treat pain adequately in neonates and eventually prevent pain using the concept of pre-emptive analgesia. We have to bear in mind that major differences exist between tissue damage due to surgical procedures such as intestinal surgery in children with necrotizing enterocolitis and procedural pain such as heel lances. This will have consequences for the choice of analgesic therapy since intravenous paracetamol and morphine are recommended after major surgery while paracetamol and morphine are not recommended for procedural pain [4,5]. Moreover, treating pain is important in preventing the short-term and potential long-term consequences of early life pain on development of the nociceptive system. The use of pre-emptive analgesia during the neonatal phase is thought to play an important role in the prevention of long-term side effects of pain. This is based on animal studies which have shown more negative effects of neonatal pain when pain experiments were conducted in the absence of adequate analgesic therapy [6]. However, exposure to analgesics can also affect development, and especially when administered in the absence of pain. Preclinical studies showed that negative long-term effects of postnatal opioid exposure may differ depending on whether they were given in the absence or presence of pain, with protective effects in the latter case [7–9]. Those animal studies showed degeneration of neurons, apoptosis in brain regions, impaired cued fear extinction, and impaired cognitive functioning after neonatal opioid exposure when administered in the absence of pain [7,10,11], while protective effects of opioid exposure in the presence of pain were observed such as less neurodegeneration [7–9]. With regards to pain behaviour, morphine pre-treated animals displayed significantly less hyperalgesia and recovered faster from a subsequent inflammatory insult compared to controls that did not receive pre-emptive opioids prior to inflammatory pain [8]. Consequently both pain and opioids have neurotoxic effects as found in preclinical studies and especially when animals were exposed to pain in the absence of analgesics or the other way around.

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Table 1
Overview of developmental stage of the area and mechanism of action of different analgesic compounds provided at neonatal age.

Analgesic	Area of action	Mechanism of action	Stage of development in newborn
Opioids ((remi)fentanyl, morphine, methadone*)	Periphery Spinal cord - Primary afferents (presynaptic opioid receptor) - Pain transmission neurons (postsynaptic opioid receptor) Brain stem - PAG - RVM	Inhibition of neurotransmitter release in the spinal pain gate; inhibition of nociceptive transmission by activation of opioid descending pathway [48]	Facilitatory instead of inhibitory [49]
Paracetamol	Periphery Spinal cord - Pain transmission neurons - Interneurons Brain stem - RVM	Prevention of peripheral sensitization by inhibition of cyclo-oxygenases (COX enzymes) Central action likely includes serotonergic descending pathway amongst others [50]	Serotonergic system is facilitatory instead of inhibitory [46]
NMDA antagonists (Methadone*, ketamine)	Spinal cord & supraspinal areas - Pain transmission neurons in spinal dorsal horn	Prevention of central sensitization [52]	Not assessed in somatosensory system

Abbreviations: NMDA, N-methyl-D-aspartate; RVM, Rostroventral Medulla; PAG, Periaqueductal Grey. The analgesic Methadone* functions via both an opioid and NMDA related mechanism.

The human nervous system is characterized by its plasticity in particular after birth in the newborn and throughout adolescence [12]. Structural and functional fine-tuning of the nociceptive system and spinal circuit is activity-dependent and can therefore be affected by noxious stimuli as well as exposure to analgesics occurring in neonatal life [13,14]. The underlying mechanisms of the potential effects of neonatal pain originate from the on-going brain development after birth, which is highly dependent on the balance between abundant new formation of connecting neurons and degradation of superfluous unused cells. Therefore, neuroapoptosis is a natural feature under these circumstances. Neuroapoptosis can however be increased by toxic effects of some analgesics and sedatives, such as ketamine [15,16].

Since rats are born at a relatively early stage of brain maturation [17], the nervous system of a neonatal rat pup roughly corresponds to that of a prematurely born neonate. Therefore, we have gained a large amount of information regarding the development of the nociceptive system based on preclinical animal models [18–21] (Table 1). It is important to note that translation of these results into the human situation should be done cautiously, as we cannot overlay the time-course of pre- and postnatal development between species.

We know from studies from the past that analgesics are essential in neonatal health care, improving short-term morbidity and mortality [22]. As described before, adequate pre-emptive analgesic therapy might even play an important role with regards to the long-term effects of pain [6].

Obviously, it is unethical to study the effects of pain in the absence of analgesics using placebo-controlled designs in the human newborn. Histological studies on the effects of pain and analgesics can only be conducted in animals. Besides information regarding the development of the nociceptive system in newborns, preclinical studies are very valuable in studying the long-term effects of neonatal pain. Early exposure to pain and stressful interventions have been associated with neurotoxicity in animals [6]. For example, pain induced by an invasive inflammatory reaction caused alterations in the spinal neuronal circuits at least in rodents [23], and severe inflammatory and procedural pain stimuli caused increased apoptosis in the brains of neonatal rats [7]. With regards to pain sensitivity, exposure to inflammatory pain in early life resulted in decreased baseline nociceptive sensitivity at adult age, and enhanced hyperalgesia after a subsequent inflammatory insult [24,25]. Repeated skin-breaking procedures in animals induced acute hypersensitivity but did not affect basal nociceptive thresholds later in life [14]. Despite this increase of knowledge into the effects of neonatal pain based on preclinical studies, the options for clinical measurement of pain in newborns are still limited. If we fully understand the nociceptive system of newborn children, we can treat pain with targeted analgesic therapy. This targeted treatment should also be based on our increased knowledge about developmental pharmacology and non-maturational factors that might influence the pharmacokinetics and -dynamics of analgesic therapy in newborns such as pharmacogenetics [26–28].

2. Development of the nociceptive system

Newborns are exposed to repetitive nociceptive input and are treated with analgesics during a vulnerable time frame for the central nervous system [29]. The use and effects of analgesics during this timeframe when the nociceptive system is rapidly developing is not yet fully understood. To clearly understand the optimal targets for analgesia in this developing system, knowledge of the functional development of the nociceptive system after birth is necessary.

The functionality of signalling pathways involved in pain perception of newborn infants differs from adulthood, as directly after birth, the somatosensory network still requires maturation at several levels [19,21]. In adulthood, specialized peripheral endings (nociceptors) contain nociception specific receptors responding to mechanical (Piezo1, Piezo2, TRPA1), chemical (ASICs), and thermal (TRPV1, TRPV2) stimuli. The activation of the peripheral endings of the nociceptive fibres results into enhanced generation of action potentials and transmission via primary afferents to the dorsal root ganglion (DRG) and further to the dorsal horn, an important hub of pain processing. Proprioceptive and tactile stimuli are transmitted by thickly myelinated Aα and Aβ fibres respectively, while thinly myelinated Aδ or unmyelinated C fibres transmit nociception specific signals. In the dorsal horn, the primary afferents synapse onto nociception specific (NS) or wide dynamic range (WDR) transmission neurons. In addition, excitatory and inhibitory interneurons are present throughout the dorsal horn, modulating pain transmission in a certain spinal segment. The inhibitory interneurons, containing neurotransmitters glycine and Gamma-Aminobutyric acid (GABA), are an important player in the 'pain gate', and can ensure a decrease in pain transmission once activated [30].

The nociceptive signal is transmitted from spinal cord to supraspinal areas via the spinothalamic tract. From the thalamus, nociceptive signals are transmitted to the somatosensory, cingulate, and insular cortex and the amygdala amongst other structures, where the localization, intensity and perception of pain occurs. Signals arriving in brainstem areas like the Rostral Ventromedial Medulla (RVM) and Periaquaductal Grey (PAG) lead to activation of descending pathways, which in turn modulate the nociceptive transmission in the spinal cord. In adulthood, painful stimuli that are prolonged and inescapable are particularly

effective for activating our endogenous opioid system within the PAG and the RVM, important components of the descending inhibitory control of pain in the spinal cord [31]. Deep somatic, visceral or repetitive superficial pain activates the ventrolateral PAG (vlPAG) and elicit long duration, opioid-dependent analgesia [32–34].

3. Nociception during the neonatal period

Immediately after birth, the somatosensory system undergoes postnatal maturation at peripheral and central levels. It is important to note that the nervous system of infants born prematurely is even more immature at birth and will undergo more postnatal reorganization. Primary afferents will undergo activity dependent reorganization [13]. Peripherally, sprouting and pruning of Aβ and C fibres occurs in the late prenatal and early postnatal period [13,21,35]. Additional myelination of Aβ fibres enables faster transduction of somatosensory signals during the first weeks of life [21]. In addition, the central connection of primary afferents undergoes postnatal reorganization. C fibres are the last to enter the superficial dorsal horn, sprouting into Rexed laminae I-II in late prenatal and early postnatal period [36]. After birth, Aβ axons extend into laminae I and II, and withdraw to deeper laminae (III-V) in the first postnatal weeks [13], leading to activation of the superficial dorsal horn by innocuous stimulation. Reorganization of primary afferents in the superficial dorsal horn ensures discrimination between touch and nociceptive signalling in later life. In addition, reorganization of the interneuron population in the dorsal horn develops over the first postnatal weeks, moving towards more targeted modulation of nociceptive processing. More specifically, the GABA and glycine containing inhibitory interneurons mature greatly after birth. In early life, inhibition of fast-acting glycinergic interneurons is less targeted and weaker, developing late in the postnatal period [37]. Interestingly, GABA binding on secondary neurons in the dorsal horn can lead to depolarization instead of hyperpolarization in early life, due to a high chloride (Cl-) concentration and low expression of Cl- co-transporters including potassium chloride cotransporter 2 (KCC2) [38].

Going up to supraspinal processing of nociceptive information, data from human studies become available. It is now clear that around 35 weeks of gestation, neuronal activity of the somatosensory cortex shows discrimination between nociception and touch as assessed by electroencephalogram (EEG) and Near-Infrared spectroscopy (NIRS) [20,39,40]. However, there is no doubt that infants born before 35 weeks of gestation can experience pain [22]. In addition, ample evidence suggests that most areas involved in pain processing are developed around birth, and the newborn brain should be able to process noxious information [20]. However, it is still unclear when exactly the newborn brain is capable of integrating nociceptive information into a painful experience. For an extensive review of the development of the nociceptive spinal cord and brain, the reader is referred to recent reviews on this topic [19,20].

Last to develop in the pain network are the descending tracts, which arise around 36–40 weeks of gestation. While anatomic connections of the descending dorsolateral funiculus are already present at birth as shown by animal studies, descending inhibition is functionally immature throughout the first postnatal weeks [41]. Previous studies have shown that the endogenous opioid system undergoes postnatal developmental changes, at both spinal and brainstem level [42,43]. In the spinal cord, opioid-mediated signalling is stronger in younger animals compared to adults [42]. In the adult PAG, a tonic opioid tone modulates the dorsal horn via the μ-opioid receptor (OPRM1), which is absent in younger animal [42,43].

Serotonergic projections from the RVM to the spinal cord are a major source of descending control in adulthood, facilitating or inhibiting nociception depending on the pain state or the 5-HT receptor subtype that is activated [44]. Serotonergic fibres grow diffusely into the dorsal horn in the term newborn. In the postnatal period, the exuberant sprouting will be pruned and will resemble the adult distribution from P21 on in rodents [45]. A recent paper assessed the development of the descending serotonergic modulation [46]. In early life, the serotonergic descending system facilitates both nociceptive and tactile processing, whereas over the first postnatal weeks this system matures and a switch from facilitation to predominant inhibition of nociception takes place [46]. This is most likely related to functional development of the spinal 5HT receptors [46]. Overall, it is clear that the spinal-bulbo-spinal loop from the RVM is active in early life, but descending modulation arises from spontaneous activity first. Later in development, modulation is mediated by ascending input, and adult patterns start to appear [47].

Box 1 – how do we study postnatal development of the somatosensory system in animals?

To study postnatal development of the somatosensory system, several methods are utilized. A large body of evidence has emerged from rodent studies, which are used as a model for premature (human) births as described before. The development of the nociceptive system in newly born rat or mouse pups resembles the human nociceptive development in its third trimester, and can therefore be used to model prematurely born infants from 24 to 37 weeks of gestation. In rodent models, knock-out or lesion models are used to study the role of a single receptor or a single system in development. In addition, in vivo electrophysiology or electromyography (EMG) are used to assess neuronal activity, and can be related to human EEG or NIRS experiments. To assess neuronal activation after pain in rodents, several pain models are utilized. Acute pain can be studied by injection of irritable, inflammatory chemicals like carrageenan, formalin, or complete Freud's adjuvant [18]. Infliction of tissue damage, either by skin incision in the hind-paw, removal of skin, or needle prick, is used to model different procedural pain modalities. Mechanical sensitivity in newborn rodents can be assessed by dorsal application of Von Frey filaments. In addition, (ultrasonic) vocalisation can be used to assess 'comfort' of newborn rodents. For an extensive review of preclinical pain models, the reader is referred to Schwaller et al. [18].

Box 2 – how do we study pain in newborns and children?

Pain assessment in the Neonatal Intensive Care Unit (NICU)

Since pain is always subjective, self-report would be the golden standard. However, as mentioned before, this is impossible in newborns. Therefore observational and behavioural pain scales have been implemented as the current best practice to assess pain in newborns and young children [2,3]. During the last 25 years many different pain assessment tools have been developed showing significant overlap and redundancy of the individual items present in the different pain assessment instruments. To determine acute and procedural pain in preterm and term born children the Premature Infant Pain Profile (PIPP) can be used. The PIPP is validated for both preterm and term born children to measure pain with good construct validity and excellent inter- and intrarater reliability [53]. The PIPP score is based on both physiological and behavioural parameters in newborns. Another very sensitive tool to measure acute pain in newborns is the Neonatal Facial Coding System (NFCS) measuring facial expressions, but only suitable for retrospective analyses of videotapes in research settings [54]. A well-known and often-used scale is the COMFORT(NEO) behaviour scale. This scale is reliable to assess prolonged acute pain and discomfort in newborns [55]. It measures the level of alertness, calmness, respiratory response, crying, physical movement, muscle tone and facial tension of a child. A different commonly used behavioural scale is the Face, Legs, Activity, Cry, Consolability (FLACC) scale. The FLACC is used to quantify pain behaviour and has a high interrater reliability [56]. However, there are insufficient data to support the FLACC scale for use in all circumstances and all

populations to which it is currently applied [2]. Despite the high number of available behavioural pain assessment tools they all have their limitations, often only presenting a snapshot of the patient's condition and are not validated to assess the response to analgesic therapy or fail to identify sensitivity to change [57].

Other techniques that hold the promise to improve the measurement of pain in newborns are near-infrared spectroscopy (NIRS), skin conductance and amplitude integrated electroencephalography (aEEG) or cerebral function monitoring (CFM). NIRS measures changes in cerebral haemodynamics in newborns and could detect the effects of painful stimuli on cortical areas of children [58,59]. Newer techniques, such as the Newborn Infant Parasympathetic Evaluation Index (NIPE™), that is based on heart rate variability, still need further evaluation [60].

The lack of a golden standard to measure pain complicates the development of better ways to assess pain in newborns. A previous study compared the Neonatal Facial Coding System with the NIRS and skin conductance in neonates during a painful stimulus [61]. This study showed that during a painful stimulus, NFCS was mildly or moderately correlated with skin conductance and cortical NIRS changes. Previous studies demonstrated that aEEG registration could show evoked responses during pain [40]. While NIRS and aEEG are non-invasive techniques for monitoring pain responses in neonates, these techniques require trained staff to conduct and interpret the recordings. Behavioural and physiological measures are advantageous to aEEG and NIRS for clinical assessment of pain in neonates [62]. Therefore, behavioural pain scales currently still are the most commonly used tools to assess pain at the neonatal care unit. However, premature infants with relatively immature nervous systems display non-discriminative facial behaviours to equally salient noxious and non-noxious inputs, presenting challenges for the interpretation of pain and analgesia in this unique patient group [63]. Future studies on the assessment of pain at the NICU in premature newborns are needed.

Due to the fear for side effects of pharmacological agents, including analgesics and sedatives, their use in the NICU is rather limited. Preterm neonatal care has focussed on non-pharmacological techniques to improve the comfort and development of the preterm infants. For instance, the use of oral sucrose to reduce pain responses to procedural neonatal pain has been thoroughly studied and is currently widely implemented. Its effectiveness in decreasing pain stimuli has been discussed and it is unclear if sucrose could help to reduce the long-term negative consequences of repetitive pain exposure in preterm infants [64].

Experimental pain tests beyond the neonatal period

Besides techniques to measure procedural, acute and chronic pain in newborn patients at the NICU, several tools are developed to measure pain thresholds and pain processing for research purposes. For experimental purposes in children and adults, quantitative sensory testing (QST) is often used to measure detection- and pain thresholds. For instance QST can be used in order to study the potential long-term effects of neonatal pain and opioid exposure [65–68]. QST encompasses a group of assessments with the goal to systematically and quantitatively test the functioning of the nociceptive system. Depending on the type of stimuli, both large myelinated and small myelinated nerve fibres in combination with unmyelinated nerve fibres can be tested, because thermal, pressure, vibration and electrical stimulation can be involved [69]. A commonly used test to determine pain intensity and tolerance is the cold pressor task [70–72]. During this task children immerse a hand or forearm in cold water and give pain scores for the duration of the test. These scores reflect the pain intensity experienced. Furthermore, the immersion time gives information about the tolerance of pain [71,72]. However, it is a qualitative test instead of a quantitative sensory test. The Neurometer (Neurotron, Inc., Baltimore, MD, USA) allows for electrodiagnostic sensory nerve testing [73] but is very painful and therefore unethical to use in children. Moreover, the flexion withdrawal reflex can be assessed using von Frey filaments to test the withdrawal reflex with different thresholds (in milli-Newton). This test can even be used in young children. In premature infants, the flexion withdrawal reflex showed a continuous threshold increase with increasing postnatal age, reflecting changes in spinal cord excitability [74]. In order to test all the different nerve fibres related to detection and pain (Aα, Aβ, Aγ, Aδ, B en C), it would be best to use thermal, electric and chemical stimuli to determine pain sensitivity. However, most of the above-described tests are not possible to conduct in young children because of ethical reasons.

Neuroimaging techniques can used as well to measure brain activity during pain in children such as functional MRI (fMRI). FMRI was first described in 1990 by Ogawa and colleagues [75,76] and detects brain activation based on the blood oxygen level dependent mechanism. It is used frequently for research purposes. Functional MRI can be used to measure brain activation in patients suffering from chronic pain but also in order to measure brain activation during painful stimuli [65,67,77,78]. However, fMRI is currently only usable for research purposes and not yet for clinical purposes to assess pain in children.

4. Pain treatment during the neonatal period

The World Health Organization (WHO) developed a three-step ladder for analgesic therapy [79]. Interestingly, this ladder was designed to treat cancer pain in adults but is very often used in children. The first step of the ladder consists of a non-opioid. In newborns, paracetamol (also known as acetaminophen) is often used as first step. For infants older than 3 months of age a non-steroidal-anti-inflammatory drug (NSAID) such as Ibuprofen can be added. In preterm newborns, NSAIDS are used with caution because of the potential side effects. Ibuprofen and indomethacin are only used in order to close a patent ductus arteriosus. Next, a weak opioid such as Tramadol is added. However, in newborn children it is not recommended to use tramadol since it is only registered for children from 1 year of age onwards. The last step consists of strong opioids such as Fentanyl of Morphine. Both Fentanyl and Morphine are commonly used on the Neonatal Intensive Care Unit [29].

4.1. Paracetamol/acetaminophen

'N-acetyl-para-aminophenol' better known as paracetamol in Europe, or acetaminophen in the United States, is the most widely used drug for pain relief in newborns. Its use has been increased by the availability of an intravenous preparation. The mechanism of action is complex and includes the effects of both the peripheral (COX inhibition), and central (COX, serotonergic descending neuronal pathway, L-arginine/NO pathway and cannabinoid system) anti-nociception processes and so-called redox mechanism [80]. Debate exists about the primary site of action of paracetamol, which may be by inhibition of prostaglandin synthesis or through an active metabolite influencing cannabinoid receptors [81].

Paracetamol prevents peripheral sensitization and has an important central analgesic effect that is mediated through this activation of descending serotonergic pathways (Table 1). However, in newborn children the serotonergic system is more facilitatory instead of inhibitory [46]. The selectivity of serotonergic control of spinal somatosensation changes with postnatal age. Preclinical studies showed that in young animals the descending serotonergic control is non-selective and amplifies the saliency of low and high-threshold mechanical sensory inputs in the spinal cord. This occurs both by increasing neuronal activity and spatial receptive field sizes of dorsal horn neurons [82].

It has been shown that the use of intravenous acetaminophen reduces the use of morphine after surgery in neonates and is therefore the analgesic of first choice after surgery in neonatal life [4]. Major differences exist regarding the labelling of acetaminophen under the age of 1 year. When dosed adequately, acetaminophen is a poor procedural analgesic but it is very effective for mild-to-moderate pain with its

additional morphine-sparing effects [83]. Moreover, in preterm born children a single dose during painful procedures showed no analgesic benefit [84], and it is generally believed that paracetamol is not an appropriate drug to treat procedural pain in newborns [85]. Interestingly, pre-emptive rectal paracetamol after assisted vaginal delivery was even associated with increased pain responses 2–3 days later during procedural pain [86]. Large studies on the pre-emptive use of paracetamol or on the potential long-term effects of paracetamol are needed [85]. Especially since previous studies showed potential associations and causal links between paracetamol exposure and neurobehavioral issues, increased incidence of atopy and reduced fertility [83].

4.2. Opioids

Opioids such as morphine, fentanyl, and remifentanil are commonly used in newborns. With respect to opioids, opioid receptors play a direct role in human neuronal development including neuronal migration, differentiation and maturation [87]. Opioid receptors are very important for normal brain development and therefore it is plausible that administration of high dosages of opioids during a period of rapid brain development will have adverse effects [87]. There are indications that opioids affect the dendritic architecture, neuronal density and μ receptor density [87]. Endogenous opioids β-endorphin and enkephalins (met- and leu-enkephalin) or analgesic drugs such as morphine or fentanyl can produce powerful analgesia by inhibiting the firing of nociceptive neurons in the dorsal horn of the spinal cord [31]. The μ-opioid receptor (OPRM1), the most potent target for analgesia, is distributed throughout the central nervous system with a high density in the dorsal horn (Table 1). Opioids activate the descending pathway from the brainstem by suppressing the inhibitory control of local GABAergic interneurons in the RVM and PAG, thereby activating projection neurons that in turn inhibit nociceptive transmission at the pain gate [31]. For an extensive review of nociceptive processing, the reader is referred to Refs. [48,52]. From studies in children with neonatal abstinence syndrome (NAS), we know that different polymorphisms in the μ-opioid receptor affect the incidence and severity of NAS [88]. Moreover, ontogeny plays an important role in the need for different dosing regimens of opioids [89]. The membrane ATP binding cassette efflux transporter P-glycoprotein expression at the meningeal blood-brain barrier is incomplete in the newborn period, but increases rapidly after birth and reaches adult levels in a few months of life. The limited expression in new-borns may allow drugs to be proportionally (brain/plasma ratio) higher in the brain. As a consequence, this may lead to an increased sensitivity to opioids, unrelated to the plasma concentration [89]. Moreover, based on animal studies we know that the endogenous opioid system undergoes crucial refinements in the descending pain modulatory pathway during postnatal development [42].

While intravenous morphine is administered to ventilated premature newborns in case of severe pain, it is not recommended to administer oral morphine to non-ventilated premature infants for procedural pain because of respiratory side effects without analgesic efficacy [5]. Next to that, morphine is not a suitable drug for short painful procedures, because of its pharmacological properties with a slow onset of action and a long half-life. Regarding preterm born ventilated children two large randomized controlled trials failed to show a positive effect of routine administration of morphine [90,91]. Studies on fentanyl and remifentanil are yet inconclusive [92]. Both drugs might be appropriate to treat severe painful procedural pain in newborns.

4.3. Other analgesic drugs

Methadone activates the opioid receptor similar to morphine, but it also blocks the N-methyl-D-aspartate (NMDA) receptor. Ketamine is another NMDA receptor antagonist. NMDA blockade is hypothesized to produce acute upregulation of the NMDA receptor, discontinuation of the NMDA receptor blocker is hypothesized to lead to excitotoxic neurotoxicity [87]. Not all NMDA antagonists induce apoptosis, however, and cell death can also occur during the NMDA blockade [87]. Therefore, the exact underlying mechanisms are not yet unravelled.

5. Conclusions

Treatment of pain in newborns, whether term or preterm born, remains a subject for improvement. Especially because the fear for negative short-term effects of pain such as increased morbidity and the fear for long-term effects with respect to neurocognition and pain processing. Even though research has made a big step towards understanding the development of the nociceptive system and the potential long-term effects of pain in newborns in the last decade, optimal and uniform treatment targets and algorithms are still needed.

In addition, the use of pre-emptive analgesia during the neonatal phase is thought to play an important role in the prevention of long-term side effects of pain. Future research should focus on the development of pain measurement techniques for clinical purposes. Moreover, research focussing on the assessment of maturational changes in the nociceptive system in a clinical setting is necessary. Finally, validation of translational measurement methods is needed in order to optimally study the effect of pain and analgesics in different stages of development. Age specific analgesic therapy based on postmenstrual age should be considered by incorporating information on the developmental stages of the nociceptive system in combination with knowledge from pharmacokinetic and –dynamic studies in newborns.

Practice points

- Pain in newborn children should be prevented or adequately treated due to negative short- and long-term consequences.
- The use of pre-emptive analgesia during pain in the neonatal phase is thought to play an important role in the prevention of long-term side effects of pain based on animal studies.
- Observational and behavioural pain scales have been implemented as the current best practice to assess pain in newborns and young children.
- Paracetamol or acetaminophen is a poor procedural analgesic but it is very effective for mild-to-moderate pain and has additional morphine-sparing effects in newborns.
- Morphine is not recommended for short painful procedures, because of its pharmacological properties with a slow onset of action and a long half-life.

Research directions

- Development of optimal and uniform treatment targets and algorithms focusing on targeted age specific analgesic therapy.
- Development of new pain measurement techniques for clinical purposes in newborns.
- Optimizing translation between clinical and preclinical pain measurement by utilizing similar techniques.
- Mechanism finding research in animal models is needed to assess maturational stage of treatment targets throughout development in order to further optimize treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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