⬡ Special Article

The Neurobiology of Infant Pain: Development of Excitatory and Inhibitory Neurotransmission in the Spinal Dorsal Horn

Damian Pattinson, B.Sc., and Maria Fitzgerald, Ph.D.

The field of pediatric pain is a relatively new one, but its importance should not be underestimated. Pain is not restricted to mature organisms, and even the youngest infants display an acute pain response that requires treatment and alleviation. Pain from invasive procedures in intensive care and postoperative pain and pain from disease and trauma are still poorly managed in infants and children, and when analgesics are prescribed, there are little data on their effectiveness. Adequate pain management in these patients has been handicapped by lack of knowledge of developing pain pathways and their response to analgesics.[1,2]

The Importance of Understanding Neurotransmission in the Context of Developing Pain Pathways

An understanding of the developmental neurobiology of nociception, particularly in the area of synaptic connectivity, is fundamental to the field. Evidence suggests that in the postnatal period, synaptic connections within the spinal cord dorsal horn undergo considerable growth, reorganization, and maturation and that pain processing in infants needs to be investigated in the context of normal developmental neuronal plasticity.[3] Behavioral and neuronal responses to nociceptive and non-nociceptive stimuli in young mammals, including humans, are clearly not under the same precise control as in the adult, leading, at spinal cord level, to lower thresholds and greater amplitudes of response and a higher degree of variability.[3,4] The reasons for this lie in the immaturity of the underlying circuitry.

Because most mammals display alterations in nociceptive processing during development, it is possible to use animal models as a means of studying changes occurring in children. Although precise correlations between the ages of rodents and humans are limited in their validity, it is generally believed that the first week of a rat's life corresponds to gestational weeks 24 to 40 in humans.[5] The rat has a 3-week gestation period, and the pups reach adulthood by 6 weeks, so, although direct comparisons are difficult to make, it can be taken that animals younger than 6 weeks are still in a physiologically immature state.

Acute pain is triggered by intense primary afferent nociceptive input, which activates neurons in the dorsal horn of the spinal cord. However, less than 10% of these dorsal horn neurons are projection neurons that send information up to higher centers in the brain; the rest are interneurons responsible for the integration and modulation of afferent evoked activity together with that from descending inputs and local networks.[6] It is the inhibitory and excitatory patterns of synaptic activity within these neuronal populations that determines the final output of the dorsal horn to higher centers in the brain, and it is here that we will find the key to the differences in nociceptive processing in the young and adult central nervous system (CNS).

This review focuses, therefore, on the postnatal development of major excitatory and inhibitory ionotropic transmitter/receptor pathways activated by nociceptive input to the spinal cord dorsal horn of the rodent. In addition, the functional implications of the postnatal maturation of these transmitter/receptor systems for pain processing are discussed. The aim is to highlight areas that may have

From the Department of Anatomy and Developmental Biology, University College London, London, United Kingdom.

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Reprint requests: Maria Fitzgerald, Ph.D., Department of Anatomy and Developmental Biology, University College London, Gower Street, London N6 4HP, United Kingdom. E-mail: m.fitzgerald@ucl.ac.uk

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important implications for the assessment and treatment of pediatric pain.

The Development of Excitatory Glutamatergic Activity in the Dorsal Horn

Most fast excitatory transmission in the spinal cord dorsal horn is mediated by the transmitter glutamate acting on postsynaptic ionotropic or channel forming receptors (iGluRs). There are 3 types of ionotropic receptors sensitive to glutamate: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and kainate (KA) receptors. Glutamatergic synaptic currents are clearly evident in the superficial dorsal horn around birth in rats,[7] including those synapses due specifically to glutamate release from nociceptive primary afferent terminals.[8] The frequency of both background and nociceptive afferent-evoked miniature excitatory postsynaptic currents increases with postnatal age, particularly between postnatal day (P) 5 and 10, probably because of an increase in the number of synaptic release sites or age-dependent changes in the probability of transmitter release.

AMPA Receptors and the Developing Dorsal Horn

Postsynaptic AMPA receptors are the main contributors of fast excitatory transmission in the dorsal horn. They are made up of a number of subunits, GluR1-4, arranged in a heterotetrameric fashion, each of which is expressed as at least 2 splice variants. The inclusion of particular subunits can drastically alter the functional properties of the receptor, for example, by allowing the channel to be permeable to calcium as well as sodium ions or by altering its ability to open at certain membrane potentials.[9]

Developmental regulation of expression of AMPA subunits. There is a high level of AMPA receptor expression in the newborn dorsal horn followed by a downregulation in the total number of AMPA receptors from birth to adulthood. Autoradiographic studies have shown that total binding of radiolabeled ligands is reduced to approximately one fifth in the adult dorsal horn with respect to the neonate.[10] In addition, the expression of AMPA receptor subunits changes during development of the dorsal horn. In situ hybridization studies show that, at birth, the most prominent subunits in the dorsal horn are GluR1, 2, and 4.[11] During development, the levels of GluR1 and GluR4 messenger RNA decrease by approximately 50%, whereas the levels of GluR2 decrease by 30%, such that the adult GluR2:GluR1/4 ratio is significantly higher. However, immunohistochemical data show a lack of GluR4 in the dorsal horn, suggesting that posttranslational mechanisms may regulate this subunit during development.[10]

Table 1. Comparison of Expression Levels of Glutamatergic Receptor Subunits in the Rodent Dorsal Horn During Postnatal Development

	P0	P14	Adult
AMPA			
GluR1	+++	+++	++
GluR2	+++	+++	+
GluR3	+++	+++	+
GluR4	+	++	+
Kainate			
GluR5	++	+	−
GluR6	++	+	−
GluR7	++	+	−
KA1	+	+	−
KA2	+++	++	−
NMDA			
NR1	++	+++	+++
NR2A	+	++	++
NR2B	++	+++	++
NR2C	−	−	−
NR2D	++	+	−

Similar findings have been obtained by using Western blot analysis, showing higher levels of AMPA receptor expression at P0 than in the adult.[12] Specifically, GluR1 and 2 are both highly expressed in the cord at P0, remain high for the first 2 weeks of postnatal life, and then decline to approximately one fifth of P0 levels by P35. GluR4 starts at relatively low levels and increases to a peak at around P14, before declining to P0 levels by P35 (Table 1).[12]

Functional aspects of AMPA receptor development. Overexpression of AMPA receptors during early development suggests increased excitatory drive at these ages, which is consistent with the high level of dorsal horn neuronal excitability in the postnatal period.[3] There is no change in glutamate excitatory postsynaptic current amplitudes in postnatal dorsal horn lamina II neurons over the postnatal period,[8] but this may not be true of all neuronal types.

An important functional aspect of AMPA receptor development is the changing ion permeability that accompanies alterations in subunit composition. Unlike NMDA receptors, AMPA receptors are not usually permeable to Ca^{2+} because of the incorporation of at least one edited GluR2 subunit in the receptor tetramer.[13] However, receptors lacking the GluR2 subunit allow Ca^{2+} ions to enter the cell at normal resting potentials (rather than the depolarized potentials required for entry through NMDA receptors and voltage-gated calcium channels). The importance of such calcium permeability is that enough calcium may enter the cell through some AMPA receptors to drive downstream changes associated with growth and synaptic plasticity.[14]

The increased ratio of GluR2 to GluR1/4 that occurs over postnatal development indicates a relatively greater number of calcium-permeable AMPA receptors in young dorsal horn and an increase in the number of calcium-impermeable AMPA receptors as the animal matures. In many brain areas, there is indeed a dramatic decrease in the number of calcium-permeable AMPA receptors over this period,[15,16] but studies in cultured embryonic spinal neurons suggest that, under these conditions at least, calcium-permeable receptor expression in dorsal horn cells *increases* during development.[17] Calcium-permeable AMPA receptors with no GluR2 subunit are found in neurons of lamina I and II_O and to a lesser extent II_I in the neonatal spinal cord,[18] and may well be important for transient changes in synaptic strength and strongly influence projection neuron firing in the neonate. However, the degree to which a cell that has been cultured for 3 weeks matches the properties of a cell from a 3-week-old cord is still unclear.

The functional effects of changing AMPA receptor subunit expression will depend on where the receptors are located. In the adult cord, cells immunoreactive for GluR1 but not GluR2 are found primarily on neurons expressing the inhibitory neurotransmitter, GABA.[19] Indeed, 78% of GluR1-positive neurons are GABAergic, whereas 97% of GluR2/3-positive, and therefore calcium-impermeable, cells are non-GABAergic. Similar findings are also obtained when using embryonic spinal neurones cultured for up to 5 weeks.[17] However, calcium-permeable AMPA receptors, although involved in modulation of inhibitory transmission, are also expressed on excitatory projecting neurokinin-1 neurons in young rats (P6-14).[18]

In summary, AMPA receptors appear to be under tight developmental control in the spinal cord. In addition to a postnatal decline in AMPA receptor expression, it appears that changes also occur to the stoichiometry, and therefore the functional characteristics, of the receptor during postnatal life.

KA Receptors and the Developing Dorsal Horn

KA receptors act alongside AMPA receptors in mediating rapid excitatory neurotransmission in the CNS. The role of postsynaptic KA receptors in mediating synaptic transmission in the neonatal spinal cord was first shown by Li et al,[20] who showed that presynaptic stimulation combined with blockade of NMDA and AMPA responses still elicited a small evoked potential in dorsal horn neurons of young rats. This response was only seen when the stimulation protocol was high enough to activate C fibers, leading them to conclude that these KA receptors were only present at C-fiber synapses. The fact that little or no KA receptor expression is seen in the adult cord implies that these postsynaptic responses are of particular importance in developing pain pathways.

Developmental regulation of expression of KA subunits. The KA receptor is made up of 5 subunits: GluR5, GluR6, GluR7, KA1, and KA2 arranged in a tetrameric fashion.[9] In situ hybridization studies have shown the presence of KA receptors in the spinal cord at embryonic day 12,[21] although binding does not occur until embryonic day 14. As with the other ionotropic glutamate receptors, KA receptors appear to follow strict developmental regulation. For example, GluR5 is expressed throughout the cord at P2, is seen only in the superficial dorsal horn by P10, and is not present at all by P21.[22] A similar profile is seen with GluR6 and 7, although at generally lower levels, whereas KA1 is expressed at moderate levels in the dorsal half of the cord in the P2 rat, appears at low levels in the ventral horn at P10, and is not seen at all by P21. KA2 is expressed at high levels throughout the cord at P2 and stays at moderate levels throughout the first 3 weeks of life, before declining so that no signal can be seen in the adult (Table 1).[22]

Functional aspects of KA receptor development. The expression of postsynaptic KA receptors in the young, but not adult, dorsal horn highlights the importance of these receptors during development, but as yet little is known of their functional significance in developing pain pathways.

Presynaptically, KA receptors have been shown to play a role in the developing thalamocortical connections of the rat whisker pathways. These synapses exhibit a short-term depression in response to a wide range of stimulus frequencies.[23] During high-frequency stimulation (corresponding to the frequency elicited by whisker activation), this depression is dependent on presynaptic KA receptors but only up to postnatal day 7, the critical period in activity-dependent modifications in the barrel cortex (the area of the somatosensory cortex receiving input from the whiskers). Because short-term depression may act to signal changes in presynaptic firing rates, this would imply an age-dependent, modulatory role for presynaptic KA receptors.[23]

Whether a similar system occurs in the immature dorsal horn, whereby presynaptic KA receptors act to modulate glutamate release on nociceptive synapses is not known. Short-term depression of transmission has been shown in the developing cord with what appears to be a presynaptic locus.[24,25] The presence of presynaptic KA receptors in the C fibers of the developing rat has been known for many years,[26] and the application of kainate to immature slices decreases AMPA and NMDA recep-

tor–mediated currents, thus showing that presynaptic KA receptors can regulate glutamate release.[27] In early development, these presynaptic receptors are permeable to calcium and switch to a Ca^{2+} impermeable form early in the first postnatal week, and it has been proposed that these Ca^{2+} permeable receptors, which are found on a subset of small C fibers, could be important in the growth of C fibers into the dorsal horn.[28] Once the synapses are formed, the KA receptors could then switch to the Ca^{2+}-independent form and allow the receptors to act as presynaptic modulators of glutamate release.

In summary, KA receptor expression represents an intriguing and relatively unexplored area of developing nociceptive pathways. A postnatal decline in receptor expression, accompanied by a marked regulation of subunit composition, suggests it has an important role in the newborn.

NMDA Receptors and the Developing Dorsal Horn

Although AMPA and KA receptors mediate fast excitatory transmission in the cord, NMDA receptors appear to contribute to slower synaptic processing, such as during repetitive stimulation. Extracellular Mg^{2+} blocks the channel at resting membrane potentials such that cations are only allowed through when there are a large number of excitatory inputs or by repetitive firing of the presynaptic input. When the postsynaptic cell is depolarized by, for example, repetitive C-fiber activity, the Mg^{2+} block is shed, the channel can open in response to presynaptically released glutamate, and ions can enter the cell. Another important property is the receptor's high permeability to calcium, not normally a feature of most AMPA or KA receptors (see earlier). Once inside the cell, these Ca^{2+} ions act as second messengers to activate intracellular signaling cascades leading to alterations in the synaptic strength. Because of this, the NMDA receptor is sometimes described as a coincidence detector for pre- and postsynaptic activity, altering synaptic strength when such coincidence occurs.[29] NMDA receptors mediate long-term changes in mono- and polysynaptic synapse strength in young rat dorsal horn neurons after high-frequency dorsal root stimulation.[30]

Developmental regulation of expression of NMDA subunits. Like AMPA and KA receptors, the structure of the NMDA receptor consists of a number of subunits (NR1, NR2A-D, and NR3A-B) arranged in a tetrameric fashion. All receptors contain 2 NR1 subunits, along with a combination of NR2 or 3 subunits. Although NR1 is thought to be essential for channel function, the NR2/3 subunits appear to play a more regulatory role, allowing for variations in receptor kinetics and sensitivity to the Mg^{2+} block. Therefore, like the other iGluRs, the function of the NMDA receptor can greatly vary depending on its subunit expression. In situ hybridization studies suggest that NR2D is the most highly expressed NMDA subunit in the rat embryonic spinal cord, with NR2B also being present.[31] This is of interest because the NR2D subunit, when recombinantly expressed with NR1, shows offset decays of between 10 and 40 times slower than any other recombinant receptors (4.8 ± 0.9 seconds for NR2D compared with 118 ± 11 milliseconds in NR2A). This could allow the receptor to detect coincidental firing of a much lower synchronicity than would be possible in the adult cord.[31] In the mouse, $\epsilon 2$ (the murine equivalent of NR2B) messenger RNA expression is found throughout the cord at embryonic day 13, but expression moves dorsally so that by P21 it is restricted to laminae I and II (Table 1).[32] The widespread expression in the neonatal period compared with older animals may be a reflection of the role of this subunit in synaptic growth and reorganization in the dorsal spinal cord.[33] Electrophysiological recordings of single channels suggest more subtle differences between the neonatal and adult dorsal horn. The technique has revealed receptors with high sensitivity to Mg^{2+} but low sensitivity to NR2B-specific antibodies, suggesting as-yet-unknown subunit compositions in the neonate.[34]

Finally, calcium-imaging studies show a decrease in calcium entry through NMDA receptors during development, implying changes in the receptor properties. Whether these changes are caused by alterations in subunit composition or by a general downregulation of receptor numbers is unclear, but interestingly, the decrease does not occur if the animals are neonatally treated with capsaicin—a process that destroys C fibers. This implies that the changes are dependent on synaptic activity.[35]

Functional aspects of NMDA receptor development. Because NMDA receptors require depolarization of the postsynaptic membrane to allow ion flow, their functional development is intimately related to that of fast transmission and AMPA receptors. Although most glutamatergic synapses have both AMPA and NMDA receptors, in young animals, synapses appear to be present that express only NMDA receptors, effectively making them "silent" at resting potentials.

Silent synapses were originally conceived by Pat Wall[36] almost 30 years ago, when he suggested that many dorsal horn synapses may not function during baseline transmission but are recruited during persistent pain. They were subsequently discovered in the dorsal horn by Li and Zhou[37] and Bardoni et al.,[7] having been previously shown to exist in other

parts of the developing brain such as the hippocampus and visual cortex.[38] Because NMDA channels have a Mg^{2+} block at resting membrane potentials, synaptic release of glutamate at NMDA receptor-only synapses will not be readily detectable and the synapse will appear silent. However, they can rapidly become functional by repetitive presynaptic stimulation. This is because high-frequency stimulation releases a large amount of glutamate, which can continually bind to the NMDA receptor and cause a gradual increase in the membrane potential. This depolarization causes the Mg^{2+} block to be removed from the NMDA channel and for Na^+ and Ca^{2+} ions to enter the cell.[37,39] The influx of Na^+ ions can even be sufficient to produce firing of action potentials.[40] The Ca^{2+} influx "unmasks" the silent synapse by triggering secondary messenger systems that cause AMPA receptors to be inserted into the membrane, thus allowing the synapse to become functional.[39]

In the brain, silent synapses appear to be under tight developmental control. For example, in the barrel cortex, they disappear by postnatal day 8—a noteworthy observation because this coincides with the end of the "critical period" of synaptic plasticity in this area.[41] However, whether such a disappearance occurs in the dorsal horn remains unclear. Although original articles were able to detect NMDA-only synapses at the end of the second postnatal week,[7] other groups have been unable to find any such synapses after P14.[42] In addition, a study performed on mice discovered the presence of NMDA-only synapses in the adult dorsal horn.[43] Whether these discrepancies are caused by species differences or from the use of different electrophysiological techniques remains to be seen.[42]

The presence of silent synapses between primary afferent terminals and dorsal horn cells could allow for a certain amount of postnatal remodelling of the system. For example, if all afferents initially form silent synapses with their target neuron, inappropriate synapses would not become stable because of a lack of coincidental postsynaptic depolarization from surrounding synapses. Those with correctly targeted inputs, however, could become stable by insertion of AMPA receptors to the postsynaptic density.[44]

In summary, the interesting properties of the NMDA receptor make it especially important in development. Its voltage sensitivity makes it highly activity dependent, and its role in allowing Ca^{2+} entry is particularly important for information storage at synapses. Expression levels, subunit composition, and colocalization with AMPA receptors all appear to be under developmental control in the spinal cord.

The Development of Inhibitory Synaptic Activity in the Dorsal Horn

Although primary afferents release only excitatory transmitters, they can produce inhibition in the dorsal horn through inhibitory interneurons. As in the rest of the CNS, fast inhibitory transmission from these interneurons is mediated by $GABA_A$ and glycine receptors, and, in common with excitatory transmitter receptors, they are under considerable developmental control. In particular, the GABA receptor displays changing subunit expressions during development, allowing it to respond in different ways to presynaptic stimuli. In addition, changes in intracellular ion concentrations and neighboring channel expression during development have recently been shown to have profound effects on the actions of these receptors.[45]

GABA Receptors in the Developing Dorsal Horn

GABA plays important roles in many aspects of neuronal development; its receptors are, in fact, present at synapses before any other. In addition, the neurotransmitter itself is present in much higher concentrations throughout the cord at birth, with approximately 50% of spinal neurons being positive for GABA, in comparison to ~15% in the adult.[46] The rate-limiting enzymes for the synthesis of GABA, glutamic acid decarboxylase (GAD), of which there are 2 forms, GAD65 and GAD67, are widely distributed in the spinal cord at birth, and, although initially thought to be downregulated in the ventral part of the cord during development,[47] are now thought the be simply redistributed away from the cell bodies to synaptic terminals.[48] Regardless of this, in situ hybridization and immunohistochemical studies do show increases in reactivity from birth until P14, followed by a decrease in overall levels, and a relocation to the superficial dorsal horn.[47,48]

Developmental regulation of expression of GABA subunits. Postsynaptically, the $GABA_A$ receptor is made up of combinations of the α, β, γ, δ, ϵ, π, or θ subunits arranged in a heteropentameric formation.[49] In the neonatal dorsal horn, the most prominent subunits, found using in situ hybridization and reverse-transcription polymerase chain reaction, are $\alpha 2$, $\alpha 3$, $\beta 3$, and $\gamma 2$. Reactivity for these subunits peaks during the first postnatal week and then declines to adult levels.[50] The most highly expressed subunit is $\gamma 2$, which is interesting because this subunit appears to be essential in postsynaptic clustering of the $GABA_A$ receptor (Table 2).[51]

Glycine Receptors in the Developing Dorsal Horn

Glycine receptors are the most abundant inhibitory receptors in the spinal cord. They are com-

Table 2. Comparison of Expression Levels of Inhibitory Receptor Subunits in the Rodent Dorsal Horn During Postnatal Development

	P0	P14	Adult
$GABA_A$			
$\alpha 2$	++	++	++
$\alpha 3$	++	++	++
$\beta 3$	++	++	++
$\gamma 2$	+++	++	++
Glycine			
$\alpha 1$	+	+++	+++
$\alpha 2$	+++	+	−
β	+++	+++	+++

posed of a number of subunits, α1-4 and β, which are arranged in a pentameric fashion[52] and show clear developmental expression profiles. In the neonatal cord, the α2 subunit is expressed throughout the gray matter, forming heteromers with the β subunit.[53,54] Although the expression of the β subunit remains high, α2 is strongly downregulated during the first 3 weeks of life (except in lamina I) to be replaced with the α1 subunit (Table 2).[52,54]

Developmental regulation of expression of glycine subunits. As with the glutamatergic receptor subunits, the glycine receptor subunits show extremely diverse kinetic properties. For example, the mean open time for α2 subunits expressed as functional channels in *Xenopus oocytes* is 174 milliseconds, whereas that of the α1 subunit is 2.38 milliseconds.[55] Accordingly, there is a developmental reduction in mean open times for glycine channels in spinal neurons and a shortening of the decay time constant of inhibitory post synaptic currents (IPSCs) in dorsal horn cells in vitro. This shortening is therefore likely caused by alterations in the subunit expression, whereby different ratios of fast and slow subunits would produce the intermediate channel kinetics observed during development.[52]

Functional Aspects of GABA and Glycine Receptor Development

GABAergic and glycinergic synaptic activity in lamina I and II over the first 2 postnatal weeks, characterized by using whole-cell patch clamp recordings, shows an age-dependent increase in the frequency of spontaneous IPSCs (sIPSCs), whereas the sIPSC amplitudes were similar in the 3 age groups. GABAergic mechanisms appear to underlie the majority of spontaneous and evoked transmission at putative inhibitory synapses in the neonate with little contribution from glycine receptors.[56]

An intriguing aspect of $GABA_A$ and glycine receptors is that in some regions of the developing CNS, they appear to act in an excitatory manner in early life, before switching to an inhibitory role during the postnatal period. This was first observed in chick embryonic spinal neurons in culture and has been subsequently confirmed in many other brain regions such as the hippocampus, cortex, and hypothalamus.[57] The change in receptor function is not related to subunit composition but to the concentration of intracellular chloride ion ($[Cl^-]_i$). During embryonic and early postnatal life, $[Cl^-]_i$ is high, which makes the reversal potential for chloride (E_{Cl}) less negative than the resting membrane potential, so that activation of the chloride-permeable $GABA_A$ and glycine receptors cause efflux of the ions and subsequent depolarization of the membrane. However, in the early postnatal period, a potassium-chloride cotransporter (KCC2) is inserted in the membrane, causing a decrease in $[Cl^-]_i$.[58] Now, E_{Cl} is more negative than the resting membrane potential, so opening of the GABA and glycine receptors produces influx of Cl^- ions and a subsequent hyperpolarization of the membrane. Indeed, the E_{Cl} in neonatal hippocampal neurons is approximately −45 mV compared with adult values of −75 mV.[59]

As with many postnatal synaptic changes, the conversion of GABA receptors from depolarizing to hyperpolarizing forms is believed to be activity dependent. The switch between excitation and inhibition appears to be brought about by GABA receptors themselves[60] because chronic blockade of GABA receptors (but not glutamate receptors or sodium channels) on cultured hippocampal neurons prevents the switch. This implies that miniature postsynaptic currents alone are capable of transforming the switch—an interesting finding because spontaneous miniture postsynaptic potentials are first seen at the same time as the switch in GABA signaling. The increase in expression of KCC2 messenger RNA is also under the control of GABA receptor activity.[60]

A similar situation appears to occur in the neonatal dorsal horn where, in 90% of E15-16 dorsal horn neurons cultured for more than a week, both GABA and glycine induced increased $[Ca^{2+}_i]$ and depolarization.[45] The depolarization and entry of Ca^{2+} through voltage gated channels by GABA receptors and glycine receptors decreases with age in culture and is gone by 30 days.[61] Ages in culture are hard to extrapolate to "in vivo" development and the timing of the switch from hyperpolarizing to depolarizing in neonatal intact dorsal horn is not known.

Inhibitory synapses in the dorsal horn undergo further alterations later in postnatal development, before becoming stable by the end of the third postnatal week. Although GABA and glycine are released from inhibitory dorsal horn interneurons simultaneously,[62] a developmental shift occurs at the postsynaptic membrane. Therefore, although

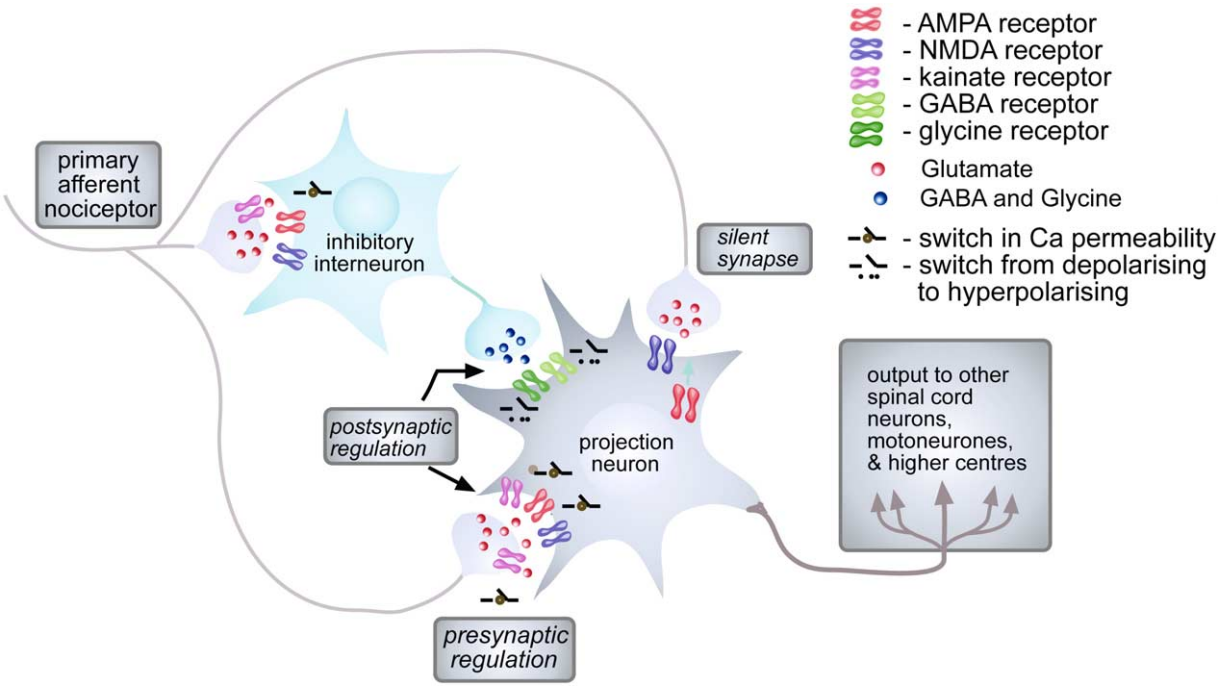

Fig 1. Diagram illustrating the synaptic basis for altered neurotransmission in the dorsal horn over the postnatal period. A simplified neuronal circuit involving a primary afferent nociceptor, an interneuron, and a projection neuron is used as an example to show how glutamate release from primary afferent nociceptor terminals onto AMPA, NMDA, and KA receptors and GABA and glycine release from interneuron terminals are under developmental control. The change in receptor function with age will alter the output of the projection neuron and therefore the pain response.

immature synapses (<P23) can codetect both GABA and glycine, the synapses of older animals can detect only GABA or glycine but not both.[63] In addition, this developmental change appears to be region specific, so that in immature lamina I mIPSCs are either GlyR only, GABAR only, or mixed, whereas in adult lamina I, mIPSCs are Gly only. In lamina II, a similar mIPSC pattern is seen in the young animal, whereas mature cell responses are 52% GABAR only and 48% are GlyR only.

In summary, the development of inhibitory neurotransmitters and receptors is highly regulated over the postnatal period, resulting in substantial functional changes at developing inhibitory synapses over this time. The impact of these changes on pain processing in the newborn is likely to be substantial.

Conclusion

The spinal dorsal horn is the first level of the CNS in which nociceptive input from sensory afferents is integrated and transmitted. Although this input is clearly present from birth, it is by no means mature and over the postnatal period substantial alterations take place in both excitatory and inhibitory dorsal horn transmission (Fig 1). Here we have concentrated on the structural and functional changes that take place in glutamate, GABA, and glycine receptors. Some, such as GABA depolarization might be expected to increase the excitatory drive in the developing dorsal horn. Others, such as changing subunit expression, may alter spatial and temporal patterns of postsynaptic activity in a more subtle way. Still others, such as the transient functional expression of postsynaptic KA receptors, suggest quite different receptor mechanisms in the neonatal cord. Importantly, many aspects of receptor development are activity dependent, implying that excessive sensory or pain activity early in development as may occur in infant surgery and intensive care may alter their maturation.[64]

These studies offer a deeper understanding of pain transmission in the youngest patients and the possibility of new targets for analgesia agents specifically designed for paediatric pain. The results show the complexity of ionotropic glutamate receptor makeup, whereby a large array of possible subunit combinations lead to substantial differences in the conductances and kinetics of the channel. The fact that different expression patterns and subunit combinations are not only restricted to different CNS regions but are also developmentally controlled over time highlights the importance of a specialized approach to the pharmacological treatment of neonatal pain.

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