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ENDOGENOUS AND EXOGENOUS OPIOID EFFECTS ON OLIGODENDROCYTE BIOLOGY AND DEVELOPMENTAL BRAIN MYELINATION

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Abstract

The elevated presence of opioid receptors and their ligands throughout the developing brain points to the existence of maturational functions of the endogenous opioid system that still remain poorly understood. The alarmingly increasing rates of opioid use and abuse underscore the urgent need for clear identification of those functions and the cellular bases and molecular mechanisms underlying their physiological roles under normal and pathological conditions. This review is focused on current knowledge on the direct and indirect regulatory roles that opioids may have on oligodendrocyte development and their generation of myelin, a complex insulating membrane that not only facilitates rapid impulse conduction but also participates in mechanisms of brain plasticity and adaptation. Information is examined in relation to the importance of endogenous opioid function, as well as direct and indirect effects of opioid analogues, which like methadone and buprenorphine are used in medication-assisted therapies for opioid addiction during pregnancy and pharmacotherapy in neonatal abstinence syndrome. Potential opioid effects are also discussed regarding late myelination of the brain prefrontal cortex in adolescents and young adults. Such knowledge is fundamental for the design of safer pharmacological interventions for opioid abuse, minimizing deleterious effects in the developing nervous system.

Keywords

oligodendrocyte development; brain myelination; opioid signaling; nociceptin; perinatal opioid exposure; opioid pharmacotherapy treatments

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Introduction

Opioid abuse and misuse continues to represent a problem of major epidemic proportions. This is particularly alarming when considering the large number of babies exposed to opioids during pregnancy, and in addition, the significant percentage of these infants that require opioids after birth for the pharmacological treatment of neonatal abstinence syndrome (NAS)[1]. Newborns affected by NAS exhibit different symptoms of variable magnitude that may include central nervous system dysfunction reflected in tremors and seizures, inconsolable crying, excessive irritability, poor sleep, and elevated muscle tone; as well as autonomic nervous system effects resulting in various digestive and respiratory problems and altered temperature regulation[2–6]. Opioids and their metabolites have the capacity of crossing the placenta[7–9] and blood-brain barrier[10,11]. Thus, NAS symptoms are logically considered to be the result of abrupt discontinuation of maternal opioid supply after birth. Current successful and necessary medication-assisted therapies for opioid addiction during pregnancy involve the administration of the synthetic long-lasting opioid analogue and full mu-opioid receptor agonist methadone; and more recently, buprenorphine, a partial mu-opioid agonist and kappa-opioid receptor antagonist that not only successfully prevents the maternal abuse of opioids but also exhibits higher efficacy than methadone in reducing the incidence and severity of NAS[12–16]. However, an increasing number of reports suggest that some of these opioid-based therapeutic approaches may also exert neurodevelopmental effects. While much is known about opioids and their role in pain regulation, the high expression levels of different opioid receptors and their endogenous opioid ligands throughout the developing brain point to the existence of maturational functions that still remain poorly understood. This raises the question of whether interference with the endogenous opioid system by exogenous opioids, including those used in pharmacotherapy treatments, could also alter important developmental brain processes. A recent large prospective study in which potential effects of other drug co-exposures and compounding factors were carefully controlled and periodically monitored, concluded that gestational opioid exposure sufficient to result in NAS also increased the proportion of neonates with reduced head circumference[17]. Notably, the great majority of those infants were born from mothers that were maintained under methadone or buprenorphine treatment. The mechanisms behind these effects remain poorly understood but different findings suggest the possibility of opioid actions on different neural cell types. For example, animal models showed that perinatal methadone exposure alters the function of dopaminergic, noradrenergic and serotonergic neurons in the neonatal and early postnatal period[18]. Furthermore, while human effects are difficult to evaluate, studies using cultured human cortical organoids indicated methadone suppressive actions on neuronal function and maturation[19]. Different lines of evidence also point to potential opioid roles on various glial cell populations[20]. This review is focused on the neurodevelopmental effects that opioids may have on brain oligodendrocytes and their synthesis of myelin, the remarkably complex multilamellar structure that not only facilitates the rapid “saltatory conduction” of nerve impulses[21] but is also now recognized as a crucial player in brain plasticity and in active bidirectional neuron-glial communications[22–24]. As such, oligodendrocyte generation and myelin formation are among the most critical and vulnerable processes that take place during brain development.

Developmental oligodendrocyte generation and brain myelin formation as direct targets of endogenous and exogenous opioids

Oligodendrocytes are generated from bipolar highly proliferative and migratory progenitor cells that experience several distinct stages of differentiation prior to their transformation into quiescent and morphologically complex multipolar cells capable of myelin formation[25]. Importantly, each of these mature oligodendrocytes has the remarkable capacity of generating multiple extensive membrane extensions that contact numerous neurons and concentrically wrap around their axons generating multiple myelin internodes. This well-defined progression along the oligodendroglial lineage assumes the orchestration of both extrinsic and intrinsic factors that regulate gene expression by a variety of mechanisms that are still the center of active investigation[26–30]. The presence of opioid receptors in stem cells and the different stages of oligodendrocyte differentiation, support the notion that the endogenous opioid system plays crucial roles in controlling oligodendrocyte maturation and suggest that interference by exogenous opioids could alter developmental brain myelination[31–34].

This represents a problem of significant developmental importance because it is now known that myelin functions expand well beyond of that as an insulator facilitating the rapid “saltatory conduction” of nerve impulses. Myelin plays a crucial role in regulating axonal extension and radial growth[35], and its presence is required for both the induction and preservation of specific localization of Na^+ and K^+ channel domains at nodal and paranodal axonal regions[36]. Importantly, oligodendrocytes and myelin are critical players in mechanisms of neuronal survival and axonal function and integrity[37,38]. Oligodendrocytes also actively participate in electrical coupling to astrocytes[39]; and together with myelin, are capable of bidirectional glial-neuronal signaling and communication[22]. Furthermore, both oligodendrocytes and myelin are actively implicated in plastic memory and learning[23,24,40–43], setting oligodendrocyte generation and myelin formation among the most critical and vulnerable processes that take place during brain development. Thus, it is not surprising that negative effects on myelin structure and stability are known to occur with the abuse of various drugs; including cocaine[44], cannabinoids[45], alcohol[45,46] and methamphetamines[47].

As discussed above, the dramatic increase in opioid use and abuse also triggered an alarming rising number of newborns that are exposed in utero to maternal pharmacotherapy treatments[48], being methadone and buprenorphine the most successful and current recommended opioid analogues for these therapies[12–16]. Yet, reports on short- and long-term neurodevelopmental effects of prenatal exposure to these drugs and other opioids are conflicting and difficult to assess as multiple interacting factors such as maternal poly-drug use or social and educational environment can profoundly influence cognitive development (recently reviewed by[49]). The complexity of these compounding factors is further emphasized by studies in rodent models indicating that adult offspring of dams chronically exposed to morphine during puberty exhibit anxiety-like behaviors and enhanced morphine sensitization[50].

In support of potential opioid effects on developmental myelination, recent imaging studies revealed white matter injury and abnormal myelin structure in the brain of infants prenatally exposed to opioids[51]. In this regard, examination of potential effects of perinatal exposure to buprenorphine and methadone indicated complex responses with significant alterations in the timing of rat brain myelination[52,53]. In these studies, pregnant rats (gestation day 7) were implanted with minipumps to deliver buprenorphine at doses of 0.3 (therapeutic) or 1 (supra-therapeutic) mg/kg/day. By using this experimental paradigm, pups were first exposed to the drug through the placenta immediately prior to brain development; and then through lactation, during a neurodevelopmental period equivalent to the third trimester in human pregnancy. Analysis at postnatal days 12, 19, and 26 (ages that respectively correspond to the beginning, peak, and end of the rapid period of myelin formation in rat brain), demonstrated that perinatal exposure to buprenorphine significantly alters their brain content of myelin basic proteins (MBPs)[52]; important myelin components that comprise about 30% of the total myelin protein and are required for the formation, compaction, and stability of myelin multilamellar structure[54]. Interestingly, these buprenorphine-induced effects were specifically dependent on the age of the pups at the time of tissue collection and the dose of administered drug. Myelin formation and growth in the mammalian brain is accompanied by a progressive increase in the expression of four major MBP isoforms generated by alternative splicing of a single developmentally regulated gene[55]. Unexpectedly, the accumulation of all MBP isoforms was accelerated and increased by exposure of the pups to the therapeutic buprenorphine dose of 0.3mg/kg/day. In contrast, supra-therapeutic levels delayed MBP expression. Furthermore, although MBP isoforms in pups exposed to elevated doses of buprenorphine finally reached control values by day 19, histological analysis of the corpus callosum fibers at 26 days of age still indicated a reduced number of axons that were myelinated[52]. Because MBPs are only synthesized when oligodendrocytes reach maturity, those findings suggested direct dose-specific effects of buprenorphine on oligodendrocyte development, a possibility supported by studies in which cultured cells directly isolated from the postnatal brain were treated with different drug concentrations[34]. Buprenorphine indeed exerts direct dose-dependent effects on oligodendrocyte differentiation, with low concentrations (0.5 μM) accelerating the transformation of immature pre-oligodendrocytes into morphologically complex MBP-making multipolar mature cells, an effect found to be mediated by mu-opioid receptor activation. In remarkable contrast, elevated drug concentrations (3 μM) block oligodendrocyte maturation, an inhibitory effect mediated by concomitant buprenorphine-dependent activation of the nociceptin/orphanin FQ receptor (NOR). Also known as opioid receptor like-1 (ORL-1), NOR is the most recently discovered member of the opioid receptor family, and while this G-protein coupled receptor shares a high degree of homology with the classical opioid receptors, it does not bind any of the endogenous opioid peptides and it is only specifically activated by the endogenous heptadecapeptide nociceptin[56]. Antagonist effects of the mu-opioid receptor and NOR were originally identified as responsible for the characteristic bell-shaped dose-response of buprenorphine effects on pain regulation[57–59]. Importantly, a number of recent publications point to the involvement of NOR and its ligand nociceptin as regulators in a variety of important processes that span from behavior, learning and memory[60–62] to drug addiction control[63,64]. Together with the *in vivo* findings, buprenorphine effects on cultured cells pointed to a model in which this drug induces direct effects by binding to two receptors with

different drug affinities and opposing roles on oligodendrocyte development. Activation of the high affinity mu-opioid receptor by low buprenorphine concentrations results in stimulation of oligodendrocyte maturation, while this positive action is counteracted by an inhibitory effect induced by high drug doses and simultaneous signaling through the low affinity NOR. Consistent with this idea, oligodendrocyte maturation is also stimulated by the mu-opioid receptor agonist methadone[53]. As observed for the low concentrations of buprenorphine, direct exposure of post-mitotic but still immature pre-oligodendrocytes to methadone results in a significant increase in the expression of different myelin specific proteins and morphological complexity. [^{3}H]Thymidine incorporation into DNA, showed that methadone also stimulates the proliferation of cultured oligodendrocyte progenitor cells[53], a finding that is in agreement with earlier reports indicating that mu-receptor activation can increase the mitogenic capacity of these still immature cells[31,65]. In agreement with those findings, electron microscopic analysis of the corpus callosum in 2-week-old pups perinatally exposed to therapeutic doses of methadone indicated accelerated myelination with abnormally elevated number of axons with already highly compacted myelin sheaths[53]. These effects of methadone and buprenorphine support an important role of the endogenous mu-opioid and NOR signaling systems in the control of oligodendrocyte maturation and the precise timing of brain myelination. In support of physiological developmental functions of the mu-opioid receptor and NOR, male and female rat brain expression levels of their respective endogenous ligands, endomorphin-1 and nociceptin are also developmentally regulated[66]. Nociceptin concentrations exhibit a significant and progressive decrease from postnatal day 9 and thereafter, reaching background levels of detection by one month of age, a pattern of expression that inversely correlates with the progression of rat brain myelination. Endomorphin-1 levels are still elevated at postnatal day 9 but gradually decrease from day 13. Just like methadone and low buprenorphine concentrations, endomorphin-1 stimulates oligodendrocyte maturation and morphological complexity. Interestingly, this stimulation is abolished by co-incubation of the cultures with nociceptin. An inhibitory effect of nociceptin in oligodendrocyte maturation and myelinating activity is further supported by the observation that *in vivo* inhibition of NOR signaling results in accelerated myelination. Surprisingly, these effects of endomorphin-1 and nociceptin are most significantly observed for the female rat oligodendrocytes and the female brain[66].

Altogether, these findings suggest that a complex balance between opposing functions of mu-opioid receptor and NOR signaling may play a crucial role in controlling the timing of brain myelination. Importantly, nociceptin also appears to have an important stimulatory role on neuronal development, as this peptide was shown to exert a supportive effect on rat cerebellar granule neurons[67] as well as positive actions on neurite outgrowth in mouse hippocampal cells[68]. Thus, it is possible that nociceptin may play a crucial double function stimulating on one side neuronal maturation while on the other hand deterring premature myelination, a situation that could interfere with early axonal elongation and neuronal connectivity. Such a situation may in part underlie the still puzzling finding from earlier studies indicating that, regardless of the dose, the brain of rat pups perinatally exposed to buprenorphine exhibited increased caliber of myelinated axons with disproportionally thinner myelin sheaths[52]. Since no differences could be found for nonmyelinated axons, that

observation suggested that buprenorphine could perhaps interfere with the mechanisms coordinating axonal outgrowth with myelin formation. Methadone-induced enhanced proliferation of oligodendrocyte progenitors and acceleration of cell differentiation and myelination may also derail the delicate balance between opposing functions of mu-opioid receptor and NOR signaling, thus altering the proper timing of brain myelination and neuronal connectivity (Figure 1).

Precocious oligodendrocyte maturation may also ultimately result in a long-term reduced pool of differentiated cells, a possibility that could at least in part explain the decreased amount of myelin protein recently reported in a different model of perinatal methadone exposure[69].

Oligodendrocyte maturation and developmental myelination as secondary targets of opioid effects

The previous section of this review focused on physiological functions of endogenous opioid systems in oligodendrocyte development and the consequences of their direct interference by exogenous opioids. However, as a logical reflection of the multiple roles and integrative functions of oligodendrocytes and myelin, important consideration should also be given to potential indirect effects mediated by primary opioid actions on other diverse cell targets. Understanding of such secondary effects could be of critical importance in the design of treatments for opioid pharmacotherapy during pregnancy and NAS. It is conceivable that effects of methadone, buprenorphine, and morphine on oligodendrocyte and myelination may also be mediated through their actions on the other two major glial cell types, astrocytes and microglia. Although this possibility remains to be examined, several lines of evidence indicate that both of these cells exhibit functional opioid receptors[70–74]. Studies with cultured cells demonstrated that morphine inhibits astrocyte proliferation[75], thus a reduction in the size of astrocyte pools at developmental times of active myelination may decrease the availability of multiple astrocyte-secreted factors which as platelet-derived growth factor (PDGF)[76–78] and neurotrophins[79–82] are known to exert modulatory effects on the oligodendroglial lineage and myelination. A decreased number of astrocytes could also limit the concentration of leukemia inhibitory factor (LIF), a molecule that controls the self-renewal and proliferation of neural stem cells and subsequent generation of oligodendrocyte progenitors[83]. Moreover, studies in neuronal-glial co-cultures showed that astrocyte-secreted LIF could directly stimulate oligodendrocytes to support myelination in response to neuronal electrical impulses[84]. It is also possible to speculate that reduced pools of astrocytes would result in decreased brain concentrations of nociceptin[85], an endogenous peptide that as described in the previous section was shown to play a function counteracting the stimulatory mu-opioid signaling effect on oligodendrocytes and thus precluding untimely precocious brain myelination[34,66]

Importantly, microglial cells could mediate negative effects of morphine on myelination. Studies in cultured cells showed that mu-opioid receptor activation by morphine stimulates the microglial secretion of interleukin-1β[72], a pro-inflammatory cytokine that disrupts developmental myelination[86]. Strongly supporting the importance of neuroinflammatory

effects, recent studies in which pups were exposed to methadone (8–16 mg/kg) from embryonic day 16 to postnatal day 21, showed a dose-dependent increased in serum inflammatory biomarkers and microglia activation, accompanied by decreased myelin protein expression[87]. This may represent a mechanism of critical importance as microglial activation and neuroinflammation have been linked to the pathogenesis of neurodevelopmental diseases such as schizophrenia[88] and autism[89].

Last but not least, there is also the important possibility that secondary opioid effects on myelination could be mediated by various primary neuronal effects. Developing oligodendrocytes express neurotransmitter receptors and are responsive to different neurotransmitter signals[90,91], therefore opioid addiction treatments could affect cell maturation and myelination through the disruption of oligodendroglial-neuronal signaling. Pioneer studies demonstrated that perinatal exposure to methadone delays the expression of the cholinergic phenotype in the striatum[92–95], reducing striatal acetylcholine (Ach) levels in neonatal rats regardless of whether or not drug exposure continues into the early postnatal period[95]. Perinatal methadone exposure also alters the function of dopaminergic, noradrenergic and serotonergic neurons in the neonatal and early postnatal period with some of these changes even persisting into adulthood[18]. Abnormal neuronal signaling to developing oligodendrocytes may also result from exposure to buprenorphine. Similar to methadone, therapeutic doses of buprenorphine were shown to accelerate the development of righting reflex[96] and prenatal drug exposures reduce striatal Ach content during the first week of life. Such altered cholinergic development may reflect methadone or buprenorphine effects on the expression of nerve growth factor (NGF), a neurotrophin that stimulates expression of the cholinergic phenotype in striatal neurons[97].

Additional support for a disruption of glial-neuronal communication by perinatal buprenorphine exposure is the observation that the corpus callosum of rat pups perinatally exposed to buprenorphine exhibited an increased proportion of high caliber axons with disproportionally thinner myelin sheaths. As discussed before, such a situation may be in part mediated by interference with the normal function of nociceptin. Interestingly, this abnormal axonal diameter/myelin thickness ratio was accompanied by increased levels of the myelin associated glycoprotein (MAG)[52], a protein that is majorly localized in the periaxonal myelin layer and may play a crucial function as a mediator of glial-axonal communication[98]. In addition, the previously described acceleration of myelination in pups exposed to therapeutic doses of buprenorphine was accompanied by increased interaction of MAG with the Src-family tyrosine kinase Fyn, a signaling molecule that mediates axonal-oligodendroglial interactions leading to myelination[52]. Thus, it is clear that much remains to be investigated to fully understand the direct and indirect effects that endogenous and exogenous opioids may have on developmental brain myelination.

Discussion

The findings described in this review point to significant opioid modulatory effects on perinatal oligodendrocyte differentiation and brain myelination. Cell culture studies and animal models of perinatal opioid exposure suggest that a complex balance between opposing effects of the mu-opioid- and nociceptin receptor activities control the precise

timing of oligodendrocyte maturation and myelinating activity[34,66]. Such balance may play and important function preventing precocious myelination, a situation that could interfere with early axonal elongation. Exogenous opioids like methadone and buprenorphine may alter this balance, a situation that would affect the time-dependent coordination of myelination with axonal outgrowth and connectivity. Furthermore, recent imaging studies determined the presence of white matter injury and abnormal myelin structure in the brain of infants that were prenatally exposed to opioids[51], supporting potential effects of these drugs on developmental human myelination.

While most of the review included evidence regarding the effects of methadone and buprenorphine, it is also particularly concerning the administration of morphine for sedative purposes in preterm neonates[99]. While little is still known about opioid effects at such young age in the human brain, studies investigating the consequences of morphine administration in the developing rat brain demonstrated about 30% reduced myelin basic protein mRNA expression induced by daily morphine administration during the first postnatal week[100]. Equally important is to consider the potential effects that chronic opioid abuse may have at later ages of brain development. Early histological analyses and imaging demonstrated that heroin and morphine abuse in adult humans can result in severe myelin damage and spongiform leukoencephalopathy[101–106]. Importantly, similar myelin damage in the adult brain could also result from acute overdose of prescription opioid painkillers. Severe leukoencephalopathy was observed in cases of acute Oxycodone intoxication[107] and Fentanyl overdose[108,109]. While these effects may potentially involve the overlooked actions of multi-drug use and other compounding factors, these observations also raise the need for studies on the effects of some of these “newer” drugs in child brain myelination as Fentanyl is used within the neonatal or pediatric intensive care settings[110]. More recently, the importance of oligodendrocytes as targets of opioid addiction at later stages of brain maturation is further supported by recent studies in which validated single-cell RNA-sequencing was used to profile cell-type-specific changes in the nucleus accumbens of adult mice four hours after acute morphine administration[111]. While both neurons and glial cells exhibited significant changes in gene expression, a remarkably strong transcriptional response was observed in the oligodendrocytes. In these particular cells, upregulation of multiple glucocorticoid receptor signaling related genes was accompanied by decreased expression of genes encoding heat shock- and endoplasmic reticulum (ER) chaperone proteins that are critical for ER quality control and the unfolded protein response (UPR). This is particularly significant as different studies showed that UPR control plays a very important role in oligodendrocyte cell survival and myelin maintenance[112,113]. Particularly disturbing in this regard are the potential deleterious effects that these drugs could have in teenagers and young adults, a population that represents the largest group for the use and abuse of prescription and non-prescription opioids[114–117]. This concern stems from the fact that a very active and extensive late wave of myelination in humans takes place in the adolescent and young adult prefrontal cortex (PFC)[118–120], a brain region that is highly interconnected with other cortical and subcortical areas and it is crucially involved in complex cognitive control and behavior[121–124]. Furthermore, myelin pathology at this age bracket has been observed in an array of psychiatric conditions, including bipolar depression[125,126] and schizophrenia[127]. Importantly, a variety of processes associated with

PFC function, including among others learning and memory, motivation, and self-control, are characteristically altered in individuals affected by drug addiction (reviewed by Goldstein and Volkow[128]).

In conclusion, the information summarized in this review supports an important role of the endogenous opioid system in controlling the development of oligodendrocytes and their myelinating activity. Studies in animal models and cultured oligodendrocytes indicate that interference with mu-opioid and nociceptin-receptor signaling systems by exogenous opioids used in drug maintenance treatments during pregnancy alters the timing of brain myelination and may therefore disrupt its crucial coordination with axonal outgrowth and synaptic connectivity. While the precise neurodevelopmental functions of endogenous opioid peptides in the developing human brain remain poorly understood, such possibilities deserve further investigation as longitudinal studies along childhood have shown a significant correlation between general cognitive ability and the precise timing and pattern of neurodevelopmental brain myelination[129]. Important in this regard are recent observations indicating abnormal microstructure of major white matter tracts in newborns exposed in utero to methadone[130], and the existence of persistent neurocognitive alterations in teenagers and young adults that were prenatally exposed to opioids[131]. Recent information on sex-specific responses to endogenous opioid and opioid-related peptides in oligodendrocytes and myelination of the female rat brain[66], stresses the need for further understanding of the molecular events mediating these functions and future studies addressing potential sex-related differences in the neurodevelopmental effects of both therapeutic opioid painkillers and opioid-pharmacotherapy treatments.

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The elevated presence of opioid receptors and their ligands throughout the developing brain points to the existence of maturational functions of the endogenous opioid system that still remain poorly understood.

The alarmingly increasing rates of opioid use and abuse underscore the urgent need for clear identification of those functions and the cellular bases and molecular mechanisms underlying their physiological roles under normal and pathological conditions

The findings described in this review point to significant opioid modulatory effects on perinatal oligodendrocyte differentiation and brain myelination

Studies in animal models and cultured oligodendrocytes indicate that interference with mu-opioid and nociceptin-receptor signaling systems by exogenous opioids used in pharmacological treatments during pregnancy alters the timing of brain myelination and may therefore disrupt its crucial coordination with axonal outgrowth and synaptic connectivity

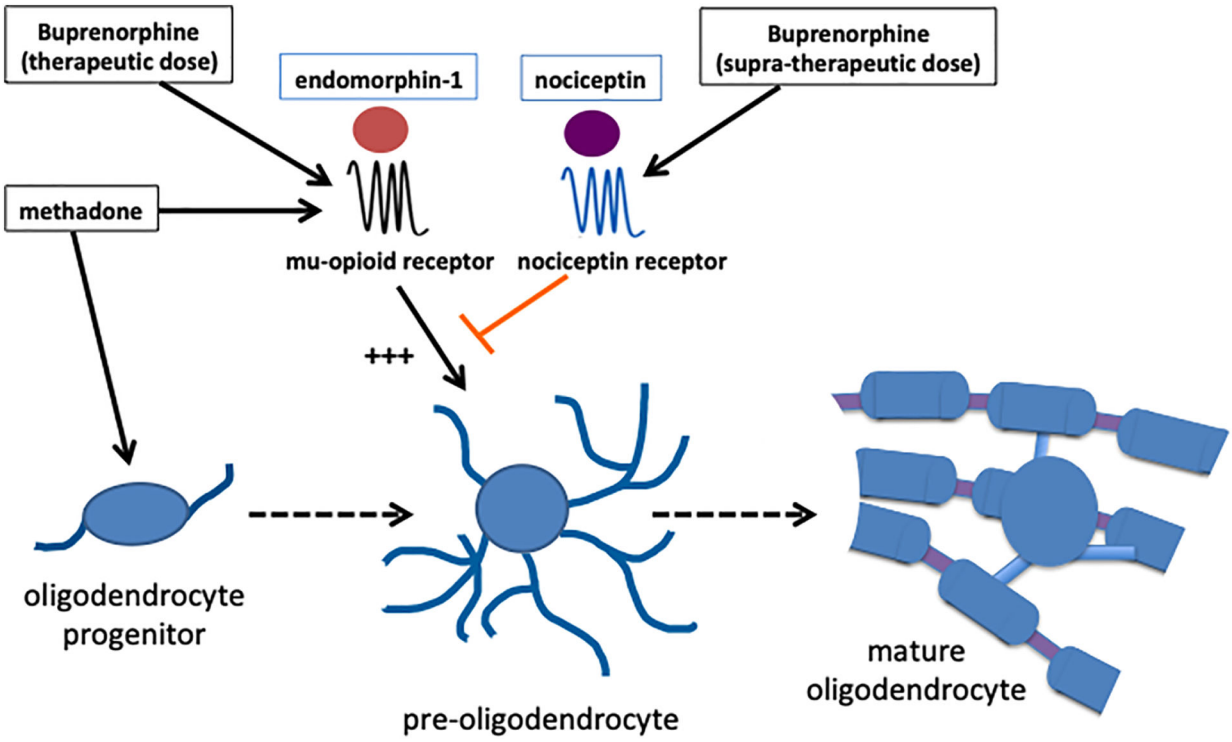

Figure 1.

A delicate balance between opposing effects of the mu-opioid- and nociceptin receptor activities appears to control the precise timing of oligodendrocyte maturation preventing precocious myelinating activity. Exogenous opioids like methadone and buprenorphine may alter this balance, a situation that could affect the time-dependent coordination of myelination with axonal outgrowth and connectivity.