The Development of Adolescent Chronic Pain following Traumatic Brain Injury and Surgery: The Role of Diet and Early Life Stress

Sabrina Salberg^a Marissa Sgro^a Rhys D. Brady^a Melanie Noel^b
Richelle Mychasiuk^a

^aDepartment of Neuroscience, Central Clinical School/Monash University, Melbourne, VIC, Australia;

^bDepartment of Psychology, Alberta Children's Hospital Research Institute, Hotchkiss Brain Institute/The University of Calgary, Calgary, AB, Canada

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Abstract

Pain is evolutionarily necessary for survival in that it reduces tissue damage by signaling the body to respond to a harmful stimulus. However, in many circumstances, acute pain becomes chronic, and this is often dysfunctional. Adolescent chronic pain is a growing epidemic with an unknown etiology and limited effective treatment options. Given that the relationship between acute pain and chronic pain is not straightforward, there is a need to better understand the factors that contribute to the chronification of pain. Since early life factors are critical to a variety of outcomes in the developmental and adolescent periods, they pose promise as potential mechanisms that may underlie the transition from acute to chronic pain. This review examines two early life factors: poor diet and adverse childhood experiences (ACEs); they may increase susceptibility to the development of chronic pain following surgical procedures or traumatic brain injury (TBI). Beyond their high prevalence, surgical procedures and TBI are ideal models to *prospectively* understand

mechanisms underlying the transition from acute to chronic pain. Common themes that emerged from the examination of poor diet and ACEs as mechanisms underlying this transition included: prolonged inflammation and microglia activation leading to sensitization of the pain system, and stress-induced alterations to hypothalamic-pituitary-adrenal axis function, where cortisol is likely playing a role in the development of chronic pain. These areas provide promising targets for interventions, the development of diagnostic biomarkers, and suggest that biological treatment strategies should focus on regulating the neuroinflammatory and stress responses in an effort to modulate and prevent the development of chronic pain.

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Introduction

All youth experience acute pain, and although many recover quickly, a significant proportion develop chronic pain. Chronic pain (i.e., pain lasting >3 months) is a growing epidemic with limited effective treatment options [1]. Pediatric chronic pain most often emerges in the adolescent period, and disproportionately affects

girls, with prevalence rates of 11–38%, roughly twice that of their male counterparts [2]. The impacts are wide-reaching and include missed school, reduced social and athletic activities, and mental health disorders [3]. Up to 60% of youth with chronic pain continue to suffer from chronic pain as adults [4]. This can lead to lost productivity in the workforce and cost the health care system billions of dollars [3]. Considering acute pain presents without any indication it will persist, the difficulty lies in catching its transition to chronic pain before it develops [5]. Given that we currently do not know why chronic pain develops and persists during this critical maturational period, this is a growing public health epidemic.

Critical Windows of Development

In order to survive, an organism must be able to adapt to its environment. These adaptations occur during critical windows of development as a result of genetics and epigenetics. This concept, known as programming theory, postulates that during critical periods of plasticity, organisms can permanently alter systems and their functions [6]. Although this can produce advantageous adaptations, this programming may be maladaptive and predispose an individual to disease if environmental conditions prenatally, or in early life, do not match environmental conditions later in life [6]. For instance, prenatal stress can program a persistently hyperactive hypothalamic-pituitary-adrenal (HPA) axis and lead to exaggerated responses to stress in offspring [6]. The brain is particularly vulnerable to input during childhood and adolescence as this is a critical window of plasticity and growth [7]. Early life factors are therefore crucial in explaining why outcomes later in life can differ when two individuals are exposed to similar experiences.

Adolescence is a critical developmental period characterized by the onset of puberty, which begins between 8 and 15 years of age with earlier onset for girls versus boys [8]. These maturational changes include the development of secondary sex characteristics, triggered by the activation of the HPA axis, as well as dramatic hormonal changes, increases in white matter volume and anisotropy, and decreases in total cerebral and grey matter volumes [8–10]. These brain changes are thought to be associated with increased myelination and synaptic pruning that refine the neurocircuitry of the brain [9, 11]. The prefrontal cortex (PFC), responsible for higher cognitive and executive functions, continues to develop into the third decade of life and undergoes significant maturation during adolescence [12, 13]. The resulting outcomes associated with these brain changes are improved executive functioning,

long-range planning, delayed gratification, and regulation of emotion [9, 11]. Behaviors such as risk taking and sensation seeking also increase, in response to increases in activity of the nucleus accumbens, a brain region playing an important role in motivation and reward [11, 14]. Further, the onset of mental health disorders peaks during adolescence, which is thought to be due to anomalies or exaggerations in typical adolescent-dependent brain changes [14, 15]. Given drastic changes that occur during adolescence, it is likely that environmental factors have significant and long-lasting effects that can permanently alter normal developmental trajectories [16].

Purpose of Review

The pain response plays a crucial role in survival, allowing for the instinctual removal of a harmful stimulus, without which tissue damage could become irreparable before it is registered [17]. Like any system, however, it can malfunction, and chronic pain can arise. Although the impact of chronic pain is substantial, the etiology remains largely unknown, and treatments are often ineffective. While numerous etiological factors have been hypothesized, this review will examine two prenatal and early postnatal factors of particular promise. Specifically, in this review we hypothesize and demonstrate that a high-fat diet and early life trauma can influence the development of chronic pain in adolescence following surgical procedures or traumatic brain injury (TBI). Given that for adolescents, surgical procedures and TBI are: (a) prospective models that can identify risk before chronic pain develops and (b) both are at-risk populations for chronic pain (exhibiting an approximate increased incidence of 20% post-procedure/injury [18–24]), these are two pain-provoking outcomes that warranted investigation. Further, the high incidence rates of both surgical procedures and TBI, suggest that advancements made within this realm have the potential to significantly reduce the lifelong burden of chronic pain.

Pain

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” [25]. The experience of pain is complex and varies depending not only on the stimulus, but also on how it is perceived by the individual. Thus, the full experience of pain is primarily measured in humans who are able to communicate their subjective experience. In contrast, nociception

Fig. 1. Simplified summary of the pain pathway and pain matrix. (1) External stimuli registered by A δ or C nociceptive fibers. (2) Signal is transduced to the dorsal horn of the spinal cord. For a nociceptive stimulus (solid line), signal crosses to the contralateral side of the dorsal horn and travels to the brain via the anterior spinothalamic tract. For a haptic stimulus (dashed line), the signal travels ipsilaterally in the spinal cord to the brain via the posterior spinothalamic tract. (3) Signal is then transduced to the brainstem where the posterior tract crosses contralaterally. (4) Signal then arrives at the thalamus, which relays to the appropriate brain regions in the pain matrix. Blue regions represent areas involved in sensory and acute perception of pain, while pink areas represent more cognitive and chronic processing of pain. S1, primary somatosensory cortex; S2, secondary somatosensory cortex; ACC, anterior cingulate cortex; PFC, prefrontal cortex.

refers to the physical process in which nociceptors are stimulated and the signal is transmitted to the brain via the pain pathway [26]. Therefore, in preclinical studies, nociception is used to describe “pain” as the animals’ responses to a stimulus are recorded, but subjective experiences are generally not measured.

Pain is most commonly registered as an external noxious stimulus by nociceptors in the affected area. When this happens, nociceptive fibers (C or A δ) become depolarized, and with enough intensity and magnitude, generate an action potential [27]. The signal is conducted into the spinal cord via the dorsal horn, then to the brain via the contralateral spinothalamic, spinohypothalamic, spinoreticular, or spinomesencephalic tracts [27]. Where the signal ends up, and the pathway it took, depends on the type of nociceptors stimulated, and which laminae the afferent nociceptor enters the dorsal horn in [27, 28]. For instance, A δ fibers are myelinated and respond to sharp mechanical or thermal changes, while C fibers are unmy-

elinated and respond to a more diffuse mechanical, thermal, or chemical stimuli [27–29] (see Fig. 1).

Several brain regions are involved in the pain pathway, termed the “pain matrix”: primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insular cortex (IC), anterior cingulate cortex (ACC), thalamus, amygdala, and frontal cortices [27, 30]. The somatosensory cortices are involved in determining the sensory features (i.e., location, intensity) of the noxious stimulus [27, 30]. The insula plays a role in detecting the intensity and laterality of any stimulus, and integrates information from different systems [27, 30]. The amygdala and ACC play a role in the affective/cognitive processing of pain, while the PFC is related to cognitive aspects of pain, such as attention, memory, and evaluation [27, 30]. The thalamus (i.e., the brain’s relay station) takes in sensory information and directs it to appropriate brain regions for processing [31].

Evolutionarily, pain plays a critical role in survival [32]. It signals the body to withdraw or stop an action if

causing damage [17]. Thus, acute pain is a healthy, evolutionarily essential process. In normal conditions, a cascade of proinflammatory substances, such as interleukin-6 (IL-6), interleukin-1 beta (IL-1 β), and tumor necrosis factor alpha (TNF α), are released following acute tissue damage, causing inflammation at the injury site [33]. This peripheral inflammation causes various enzymes, substance P, and nitric oxide to be released, further contributing to inflammation, potentiating nociception, and increasing excitability [33]. The injury site is then sensitive, encouraging the individual to avoid further contact and thus protecting it from damage.

The Development of Chronic Pain

Contrary to acute pain, chronic pain is not a normal, necessary response. It can occur with continued nociceptive stimulation in response to an unresolved physiological condition or may persist without identifiable causes [29]. In chronic pain, a persistent stimulus may cause peripheral and/or central sensitization [27]. Peripheral sensitization can be caused by prolonged inflammation, leading to hyperexcitability of nociceptors and resulting in hyperalgesia (an enhanced response to a noxious stimulus) [27]. Central sensitization occurs within the central nervous system (CNS) and may result in allodynia (i.e., evoked pain in response to a normally non-noxious stimulus) [27, 29, 33]. In this case, A β fibers are recruited, which are normally innocuous mechanoreceptors [27, 29, 33]. Thus, the factors involved in chronic pain are likely outside of the sensory acute pain pathway.

Acutely painful stimuli can lead to the development of chronic pain. Chronic pain often stems from an acutely painful incident, with pain persisting beyond the normative time of maximal physical healing [34]. Many experiences can be acutely painful; however, this review focuses on surgery and TBI as they are particularly prevalent in adolescent populations. Alarming, nearly 20% of youth will develop chronic pain post-TBI and surgery making them ideal models to prospectively understand transition from acute to chronic pain [18–24]. While the literature surrounding post-surgical pain is abundant, post-traumatic pain is less well studied, especially within the context of mild TBI and concussion.

Diet and the Development of Chronic Pain

Since 1975, obesity rates have tripled in adults and quadrupled in youth [35]. A healthy diet is crucial for maintaining an optimal balance of nutrients and overall

health. However, much of the Western world, particularly those of lower socioeconomic status, consumes an excessive amount of unhealthy fats and sugars, which can have serious health complications [36, 37]. This high-fat, high-sugar (HFHS) or “Western diet” results in spatial memory and learning problems, decreased neuronal resiliency to oxidation or other insults, and reductions in neuroplasticity and brain-derived neurotrophic factor in the hippocampus [38–40]. Further, HFHS diets have been associated with reduced synaptic plasticity in the PFC, and impaired function in the amygdala and HPA axis of adolescents [39, 41].

This HFHS “Western Diet” can lead to obesity, which is associated with an array of health issues, including diabetes, cardiovascular disease, hypertension, and osteoarthritis [36, 42]. A less evident consequence of this diet is chronic low-grade inflammation [43, 44]. Neurological inflammation results from an immune response in which microglia act to protect the CNS [44]. Microglia act via phagocytosis, engulfing damaged cells and pathogens [45]. They also release proinflammatory cytokines, such as IL-6, IL-1 β , and TNF α to protect and repair cells [46, 47]. However, persistent or over-activation of microglia, such as in response to systemic inflammation, can disrupt microglia function and become harmful [45]. Microglia can consume neurons and tissue and disrupt normal pathways. Moreover, checkpoints of the microglial inflammatory response can result in neurodegeneration [45, 46].

Maternal Diet

Maternal obesity results in increased inflammation for both the mother and the developing fetus, which can lead to cognitive deficits and adverse health outcomes in offspring [48]. With one-third of mothers entering pregnancy overweight, it is crucial to understand the resulting impact of this epidemic on developing fetuses [48]. For instance, Igosheva et al. [49] found that even before conception, oocytes of diet-induced obese mice exhibit elevations in reactive oxygen species (ROS), which propagated into zygote formation. Given the link between ROS and pain is well established; this demonstrates a possible avenue for the development of pain in offspring of obese mothers [50–53]. Further, rats born to dams fed a high-fat diet had increases in proinflammatory cytokine IL-6 and glial markers ionized calcium binding adaptor molecule 1 (Iba1) and glial fibrillary acidic protein (GFAP) in the brain [40, 54–56]. Maternal obesity may prime placental macrophage and fetal brain microglial cells to overrespond to later immune challenges [48].

These macrophages and microglia were shown to overproduce the proinflammatory cytokine TNF α in response to an immune challenge in the fetal brains [48]. This demonstrates that maternal obesity may impose long-lasting effects on the innate immune response of the offspring CNS, priming dysregulation of neuroimmune function [48]. Currently, it is evident that maternal diet-induced obesity causes microglia activation and inflammation in offspring. Given the potential for maternal diet to produce long-term alterations in neuroimmune function of offspring, it is plausible that a later injury or infection could lead to an excessive and persistent response.

Child Diet

Although maternal diet likely has an effect on persistent health outcomes, the diet of the developing child can also influence long-term trajectories. Many clinical studies have observed an association between obesity and chronic pain. Musculoskeletal pain and recurrent abdominal pain have been positively associated with increased weight [57, 58]. Although the association between obesity and chronic pain has been robustly observed in clinical populations, there is a gap in the literature regarding mechanisms underlying this association.

Nevertheless, inflammation is a likely culprit. Mice fed a diet high in saturated fats, versus a standard diet, showed proinflammatory microglia expansion, providing evidence that diet influences microglia function [59]. Although pain was not directly measured, this increase in microglia activation would likely exacerbate inflammation and influence pain outcomes. In a single study, juvenile rats fed the ketogenic diet (a high-fat, low-carbohydrate diet that has been shown to reduce ROS and inflammation) exhibited thermal hypoalgesia (i.e., decreased sensitivity to thermally derived pain stimuli), thereby demonstrating that diet can influence pain sensitivity by modulating inflammatory processes [60]. Thus, it is reasonable to hypothesize that a diet that encourages inflammation, such as the HFHS “Western diet,” may have the opposite effect and induce hyperalgesia.

Diet and Chronic Pain

Despite a link between diet and pain, there is a dearth of research on underlying mechanisms. Limited preclinical studies point to microglial activation and inflammation, with proinflammatory cytokines that activate nociceptive sensory neurons being a key factor in the transition from acute to chronic pain [61]. For example, primed microglia may play a significant role in the development of post-surgical pain. In a rodent surgery model, microg-

lia activation was prolonged, and allodynia was enhanced following a later immune challenge [62]. Microglia are macrophages of the brain, and the main form of immune defense in the CNS [63]. They protect the brain by responding to any pathological state, including injury, infection, or increased ROS [46, 63]. In a primed state, microglia can overrespond to later challenges with excessive levels of proinflammatory cytokines [62]. This exacerbated neuroinflammatory response may lead to post-surgical allodynia [62].

Similarly, in the context of post-traumatic pain, the increased inflammation and microglia activation associated with HFHS diets may increase one’s risk for post-TBI migraine and headache. Post-traumatic migraine and headaches are thought to occur in response to changes in cerebral blood flow, prolonged release of excitatory amino acids, and ionic imbalance (increased extracellular potassium and intracellular calcium) that results in cortical depression [64, 65]. Only recently was a rodent model of headache-related behavior after concussion developed, opening up the possibility for better investigation of the mechanism driving this relationship. This study hypothesized that cephalic allodynia was due to inflammatory activation and sensitization of meningeal afferents and, in turn, central trigeminal dorsal horn neurons [66]. It was posited that TBI promotes a migraine/headache phenotype that involves sensitivity to common triggers [66], which could be exacerbated by diet-induced neuroinflammation. Therefore, it is reasonable to suggest that diet has the potential to be a risk factor for the development of chronic pain and may be a promising target for new avenues in prevention, assessment, and treatment of chronic pain.

Adverse Childhood Experiences and the Development of Chronic Pain

Adverse childhood experiences (ACEs) include physical, sexual, and emotional abuse, neglect, and household dysfunction occurring early in life [67] and have been associated with cognitive, social, and emotional impairment, and more recently, chronic pain [68–70]. Such trauma can be physical or psychological, with the former’s implications in chronic pain being well established, and with growing evidence for the latter’s [68, 71, 72]. Proposed underlying mechanisms involve increased HPA axis activity due to increased stress [73, 74], which has been observed in chronic pain patients. Thus, this cumulative dysfunction may impact pain responsiveness [75].

Cortisol is responsible for initiating a rapid response to threats by maintaining high levels of glucose [17]. It does so by breaking down protein in muscle and inhibiting the replacement of calcium in bone, which is associated with an increased risk of bone fracture. In addition, increased cortisol levels can cause myopathy, weakness, fatigue, suppressed immune system, and accelerated hippocampal degeneration in aging [17, 76]. Hypocortisolism, which could be caused by prolonged stress-depletion of cortisol, has been linked to fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome [17].

Maternal ACEs

Early life stress can have a profound impact on an individual's health and may induce intergenerational dysfunction. Maternal ACEs have been associated with worse psychosocial health in offspring [77]. Further, in extreme cases, such as children of Holocaust survivors, maternal ACEs affected both the mental and physical health of their offspring [78, 79]. Not only does maternal childhood adversity affect the psychological well-being of offspring, it is associated with the incidence of traumatic events in children. For example, maternal abuse has been correlated with offspring victimization [80]. Mothers who experienced trauma often have impaired stress responses and socio-emotional functioning, which can lead to increased risk taking behavior (e.g., substance abuse) and, therefore, ACEs in their children [80]. This can lead to a viscous intergenerational cycle of trauma that, if appropriately addressed, would lead to healthier future generations.

Maternal distress directly impacted offspring pain, predicting recurrent abdominal pain [81], with increased maternal cortisol levels influencing cortisol levels in infants [82]. Similarly, prenatal stress in a rodent model increased basal levels of proinflammatory cytokines IL-1 β and TNF α , as well as reactive microglia in the hippocampus of offspring [83]. Further, these prenatally stressed mice showed increased levels of corticosterone, and increased expression of GFAP, Iba1, and TNF α in the dentate gyrus, following a later immune challenge [83]. This suggests prenatal stress promoted a basal proinflammatory state, resulting in exaggerated microglia response to a later insult in offspring.

Child ACEs

ACEs directly and adversely affect the individual experiencing them. Retrospective clinical studies have described an association between traumatic events and chronic pain [84–88]. An increase in childhood abuse correlates with more reported pain, and increased adverse

events, such as institutional care or familial financial hardship, correlate with chronic widespread pain [70, 86, 87]. For instance, childhood sexual abuse is associated with increased rates of chronic pelvic pain [88]. Psychological trauma early in life also increases levels of proinflammatory markers, such as TNF α , IL-6, and C-reactive protein, into adulthood [89]. This programming of neuroimmune function to a proinflammatory state may be due to epigenetic alteration of the HPA axis and the glucocorticoid receptor, which regulates inflammatory activity, and can lead to an exaggerated proinflammatory cytokine and microglia response to later immune challenges [83, 89, 90].

Although the mechanisms underlying the association between ACEs and pain are not confirmed, preclinical studies are beginning to tackle this gap in knowledge. By modelling neglect via maternal separation or deprivation paradigms, rodent pups are exposed to ACEs. By exposing animals to early stressful conditions, their nervous, endocrine, and immune systems adapt and program to cope with that environment [91]. However, when housed in non-stressful environments later in life, this adaptation can be maladaptive and lead to behavioral impairments and psychological symptoms, such as anxiety [91]. Results from such studies have also shown increased pain sensitivity, altered nociceptive responding, and changes to circulating levels of inflammatory markers [92, 93]. This has led researchers to hypothesize that epigenetic changes in response to the early childhood trauma may be implicated. For example, expression of both the glucocorticoid receptor, responsible for binding cortisol, and glial cells has been shown to be altered, which may lead to changes in inflammation and the development of persistent pain [92, 93]. Further evidence from animal studies supports the clinical literature, in which childhood trauma results in emotional dysfunction, whereby altered microglia activation was associated with increased anxiety-like and depressive-like behaviors (psychological factors often comorbid with chronic pain) [94, 95]. Thus, an altered microglia response can in turn modify inflammatory processes, which is emerging as a common factor in the development of maladaptive pain.

ACEs and Chronic Pain

Stress and chronic pain have a bidirectional relationship, with chronic pain being influenced by stress, and posing as a stressor itself, exacerbating poor functioning [96]. Stressful environments are strongly associated with child disability and other physical and mental health disorders [96]. The nature of ACEs suggests that survivors will experience significant psychological distress, altering HPA axis

Fig. 2. Summary of the potential mechanisms underlying the respective factors' contribution to the development of chronic pain.

function and cortisol levels [17, 73, 74]. The underlying mechanisms are likely complex but involve physiological dysregulation of the HPA axis due to prolonged stress activation [96]. Given that TBI and ACEs have both been demonstrated to significantly modify the HPA axis and in turn subsequent cortisol levels [97–99], and altered cortisol release in combination with dysfunctional hypothalamic activity has been implicated in headache and migraine pain [100], it is reasonable to postulate that ACEs could exacerbate, worsen, or prolong post-traumatic headache pain. Maladaptation due to prenatal and early postnatal stress may also influence inflammatory markers, prime microglia to overrespond, and alter gene expression, all of which contribute to increased inflammation and susceptibility to persistent pain [83, 89, 91–93, 101–103].

Similar pathogenic mechanisms may be at play in the context of post-surgical pain. HPA axis dysfunction is a hallmark characteristic of many chronic pain syndromes, with stress-induced abnormalities to HPA axis function being highly predictive of pain chronicity [104–106]. In addition, post-surgical pain is highly dependent upon circulating levels of stress hormones. For example, although in adults, post-operative pain following arthroplastic surgery could be predicted based on stress physiology (cor-

tisol and catecholamine levels, along with cardiovascular tone) prior to the surgery [107]. In addition, painful procedures in preterm neonates have been linked to reprogramming of the stress response and HPA axis, increased neuroinflammation, and cortical thinning (for review see Vinall and Grunau [108]). It is therefore plausible that ACE-induced alterations to the HPA axis would modify an adolescent's response to surgical pain in a similar fashion, thereby increasing susceptibility to the development of chronic pain.

Discussion

To summarize, ACEs increase stress and alter HPA axis function, with cortisol affecting chronic pain outcomes [17, 73, 74]. These traumatic events early in life can program changes in gene expression, cortisol receptors, and microglia response later in life [83, 89, 91–93, 101–103]. HFHS diets also influence microglia response through persistent low-grade inflammatory activation of the neuroimmune response [43, 44]. Like ACEs, diet can also program long-term outcomes, with dysregulation of neuroimmune function leading to overreaction to later

stressors [48]. Chronic pain often arises in response to an acutely painful experience, such as surgery or TBI, with proposed mechanisms involving microglia priming, ionic imbalances, altered blood flow, and inflammation, all of which result in sensitization [62, 64–66]. These areas provide promising targets for assessment and intervention, indicating that biomarkers and biological treatment strategies should focus on the inflammatory and stress responses, which may result in better management of chronic pain. See Figure 2 for summary of proposed mechanisms driving the relationship between poor diet, ACEs, and the development of chronic pain following adolescent surgery or TBI.

In conclusion, clinical research has established correlations between early life factors and adolescent pain, and preclinical research is beginning to elucidate mechanistic relationships and establish temporality. The gap in knowledge lies in elucidating neurobiological mechanisms underlying these relationships. Future studies are needed to disentangle the processes and complex interactions associated with the multiple factors that contribute to the devel-

opment of adolescent chronic pain. This will lead to more effective assessment and treatment strategies, targeting particularly vulnerable individuals, which could *prevent* the development of chronic pain before it even begins.

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Author Contributions

All authors contributed to the design, writing, and editing of the manuscript.

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