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Self-injurious behaviour in intellectual disability syndromes: evidence for aberrant pain signalling as a contributing factor

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Abstract

Background—In most individuals, injury results in activation of peripheral nociceptors (pain-sensing neurons of the peripheral nervous system) and amplification of central nervous system (CNS) pain pathways that serve as a disincentive to continue harmful behaviour; however, this may not be the case in some developmental disorders that cause intellectual disability (ID). Moreover, individuals affected by ID disorders may initiate self-injurious behaviour to address irritating or painful sensations. In normal individuals, a negative feedback loop decreases sensation of pain, which involves descending inhibitory neurons in the CNS that attenuate spinal nociceptive processing. If spinal nociceptive signalling is impaired in these developmental disorders, an exaggerated painful stimulus may be required in order to engage descending anti-nociceptive signals.

Methods—Using electronic databases, we conducted a review of publications regarding the incidence of chronic pain or altered pain sensation in ID patients or corresponding preclinical models.

Results—There is a body of evidence indicating that individuals with fragile X mental retardation and/or Rett syndrome have altered pain sensation. These findings in humans are supported by mechanistic studies using genetically modified mice harbouring mutations consistent with the human disease. Thus, once self-injurious behaviour is initiated, the signal to stop may be missing. Several developmental disorders that cause ID are associated with increased incidence of gastroesophageal reflux disease (GERD), which can cause severe visceral pain. Individuals affected by these disorders who also have GERD may self-injure as a mechanism to engage descending inhibitory circuits to quell visceral pain. In keeping with this hypothesis, pharmacological treatment of GERD has been shown to be effective for reducing self-injurious behaviour in some patients. Hence, multiple lines of evidence suggest aberrant nociceptive processing in developmental disorders that cause ID.

Conclusions—There is evidence that pain pathways and pain amplification mechanisms are altered in several preclinical models of developmental disorders that cause ID. We present hypotheses regarding how impaired pain pathways or chronic pain might contribute to self-injurious behaviour. Studies evaluating the relationship between pain and self-injurious behaviour will provide better understanding of the mechanisms underlying self-injurious behaviour in the ID population and may lead to more effective treatments.

Keywords

central sensitization; diffuse noxious inhibitory control; fragile X; pain; Rett syndrome; self-injury

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Despite the prevalence of self-injurious behavior (SIB) in many genetic developmental disorders associated with severe intellectual impairment, very little is known about the neurobiological underpinnings of this comorbidity. SIB occurs in different sectors of the normal population, but its frequency is much higher among individuals with developmental disorders that negatively influence brain function. Several recent advances in preclinical models of such disorders have led to a greater understanding of how mutations in genes that cause these diseases lead to changes in the structure and function of the central nervous system (CNS). At the same time, a greater appreciation of plasticity in the CNS as it pertains to chronic pain conditions has led to the recognition that molecular mechanisms of pain amplification are remarkably similar to those of learning and memory (Ji *et al*. 2003). Here we will summarise recent evidence for aberrant pain processing in humans affected by developmental disorders that cause intellectual disability (ID) and in preclinical models of these diseases. We will place these findings into the context of what is currently known about the initiation and persistence of SIB and discuss possible molecular mechanisms and anatomic pathways that may be disrupted in these diseases. We will outline an experimental framework for further work in this area to test the role of defective pain amplification in SIB that can potentially point to new therapeutic avenues. We will also discuss chronic pain as a potential contributing factor in SIB, which is a complex behaviour. Understanding the role of the nociceptive system in SIB may improve therapeutic outcomes.

Amplification is a key feature of pain pathways

Pain is a cortically dependent sensory experience with an affective component arising from activation of peripheral pain-sensing neurons (nociceptors). In a healthy individual, experiencing pain is important for survival. In the acute setting, activation of nociceptors and CNS neurons that receive input from these peripheral neurons elicits a withdrawal reflex from noxious insults to avoid further tissue damage. Nociceptors signal to supraspinal CNS structures involved in fear, emotion, and other components of avoidance in order to reduce the likelihood of subsequent dangerous encounters. Inflammation of a wound sensitises the surrounding area and encourages guarding of the affected tissue to allow healing. This last example involves pain amplification in which pain thresholds are decreased through multiple mechanisms. Pain amplification is part of the healthy self-protective response to noxious insult, but can be dysregulated in multiple pathologies (Woolf 2010).

Ronald Melzack and Patrick Wall were among the first to recognise that transmission of pain information from primary nociceptor to higher CNS structures was not always faithful and that a network of neurons in the spinal dorsal horn was responsible for gating pain information (Melzack & Wall 1965). We now have a much more advanced understanding of the anatomy and physiology underlying transmission of pain signals to the CNS and factors that influence the severity of perceived pain. The primary nociceptor is a single cell with an axon that extends from a target tissue to the dorsal horn of the spinal cord where it forms a synapse with a second-order neuron. The pain signal can then be transmitted directly from the second-order neuron to higher centres or be filtered by additional spinal neurons before projecting to the brainstem and brain (Melzack & Wall 1965). The pain signal is transmitted to multiple CNS structures that exert pronounced control over pain signalling by sending descending projections that inhibit or amplify the excitability of neurons at earlier stages in the pathway (Ossipov *et al*. 2010). Thus, cellular feedback loops filter pain signalling. Pain amplification can occur at multiple stages in this pathway: nociceptor firing threshold can be decreased, synaptic efficiency increased (Woolf & Salter 2000), or activity of inhibitory or amplifying descending neurons modified (Ossipov *et al*. 2010). While an exhaustive description of mechanisms responsible for pain amplification is beyond the scope of this review, we will explain two mechanisms that are dysregulated in mouse models of ID: wind-up and long-term potentiation (LTP), which represent two well defined neurophysiological

events involved in sensitization of CNS pain pathways – collectively called central sensitisation (Latremoliere & Woolf 2009; Woolf 2010).

Wind-up

When a noxious stimulus, such as tissue damage, is applied, it causes an initial stinging or sharp pain with a short latency (called 'first pain') and is followed by a more persistent pain that commonly possesses a burning quality. This so-called 'second pain' has a longer latency and is thought to be associated with wind-up of dorsal horn neurons (Price 1972; Price *et al*. 1977). Wind-up involves a progressive increase in action potential frequency in second-order spinal dorsal horn neurons with repetitive firing of peripheral nociceptors. This takes less than 1 s to begin and can be observed in most dorsal horn neurons that receive a nociceptive input. While the molecular mechanisms of windup are complex, its basic mechanisms involve glutamatergic neurotransmission and postsynaptic glutamate receptors of the N-methyl-D-aspartic acid (NMDA) type. Existing evidence points to progressive depolarisation through NMDA channels as a primary means through which frequency-dependent amplification of dorsal horn neuron firing is augmented (Dickenson & Sullivan 1987). In addition to increased input–output firing of dorsal horn neurons, wind-up can also lead to after-discharge in these neurons (continued firing despite the absence of continued input). Wind-up is commonly viewed as a primary mechanism for short-term plasticity in the nociceptive system because it takes place over such a short time-course (Herrero *et al*. 2000).

Long-term potentiation

Unlike wind-up, LTP involves an increase in synaptic efficacy that has a longer latency to onset and can persist for days to weeks and may even be permanent. As such, most work on LTP has focused on LTP as a mechanism of learning and memory. Several lines of evidence suggest that LTP occurs during learning and memory (Whitlock *et al*. 2006) and inhibition of molecular maintenance mechanisms of LTP reverse established memories (Pastalkova *et al*. 2006; Shema *et al*. 2007). Moreover, LTP is impaired in preclinical models of Rett (Moretti *et al*. 2006) and Fragile X mental retardation (FxS) (Zhao *et al*. 2005; Wilson & Cox 2007) syndromes. In terms of pain signalling, LTP has recently been recognised as an important synaptic amplifier mechanism in the dorsal horn (Ikeda *et al*. 2006; Sandkuhler 2007). While LTP can be induced in dorsal horn neurons by artificial high-frequency stimulation of nociceptors, it can also be observed after natural stimulation that mimics persistent inflammation and/or injury to the peripheral nervous system (Ikeda *et al*. 2006) pointing to the physiological importance of this type of plasticity in chronic pain states. While the ability of LTP to explain the full sequelae of chronic pain symptoms is still controversial (Latremoliere & Woolf 2010; Sandkuhler 2010), it is, nevertheless, a critical amplification mechanism for pain pathways that leads to enhanced pain perception in human subjects (Klein *et al*. 2004; Lang *et al*. 2007).

The significance of these mechanisms for organism fitness is reflected in their evolutionary conservation. Several studies have demonstrated that wind-up can be observed across divergent vertebrate species (Herrero *et al*. 2000), indicating that it is an evolutionarily conserved mechanism for amplifying incoming pain signals. Similarly, an LTP-like mechanism, termed long-term facilitation, can be observed in sea snails and shares molecular mechanisms with mammalian LTP (Martin *et al*. 1997). While this neurophysiological event has been extensively studied as a primitive learning and memory mechanism, it is evoked by a painful stimulus and its behavioural endpoint is a facilitation of a withdrawal reflex. Hence, pain amplification mechanisms are evolutionarily conserved across the animal kingdom in both their short- and longer-term forms. As pain is ultimately a teaching signal for limiting the extent of injury and promoting protection of an injured site

(Woolf 2010), these amplification mechanisms serve an important evolutionary purpose in protecting the individual.

Evidence for altered pain sensation and/or pain amplification in developmental disorders where self-injurious behaviour is observed

While the status of wind-up and LTP has not been examined in ID patients that engage in SIB, we anticipate that sensitisation due to wind-up and/or LTP would strongly discourage SIB. Moreover, it is formally possible that deficits in overall pain perception might allow increased incidence or persistence of SIB in the ID population. Here we will review evidence for changes in global pain responses and/or amplification of pain signalling in two genetic disorders where SIB is commonly observed, Rett syndrome (Sansom *et al*. 1993; Matson *et al*. 2008) and FxS (Symons *et al*. 2003; Hall *et al*. 2008).

Rett syndrome

Rett syndrome is an X-linked disorder caused by mutation in the methyl-CpG-binding protein 2 (MeCP2) gene (Van den Veyver & Zoghbi 2000). MeCP2 is a DNA binding protein that modifies the transcription of multiple gene targets. One significant gene target for MeCP2 is the brain-derived neurotrophic factor (BDNF) gene. Loss of MeCP2 results in decreased BDNF gene expression and this is associated with several neurological deficits in the disease. Interestingly, overexpression of the BDNF gene in a mouse model of the disease ameliorates several key deficits, while complete loss of BDNF and MeCP2 leads to enhanced disease progression (Chang *et al*. 2006). BDNF plays a key role in neuronal development and is an important factor for synaptic plasticity at adult synapses (e.g. LTP). As such, deficits in LTP are found in the mouse model of Rett syndrome (Moretti *et al*. 2006). Moreover, MeCP2 has been found to play a key role in pain plasticity (Géranton *et al*. 2007, 2008). In a preclinical model of inflammation, enhanced nociception was associated with increased phosphorylation of MeCP2. This MeCP2 phosphorylation correlated with derepression of several established gene targets suppressed by MeCP2 and these gene targets were further shown to play a causative role in the onset of inflammatory pain in this preclinical model. Although pain amplification mechanisms have not been examined in mice lacking the MeCP2 gene, mice harbouring a transgene that leads to a 50% reduction in MeCP2 expression do show deficits in acute thermal pain thresholds (Samaco *et al*. 2008). These preclinical investigations led to a close examination of potential decreases in pain sensitivity in humans with Rett syndrome. A large survey of families enrolled in the Australian Rett Syndrome Database found that decreased pain sensitivity, as measured by parental recall, was a common feature of Rett syndrome, suggesting that these preclinical findings may indicate a disruption in pain signalling in the human population (Downs *et al*. 2010). Further studies to assess pain thresholds will be required in this population. The potential intersection of decreased pain signalling and/or amplification with SIB in this disease has not been examined.

Fragile X mental retardation

Fragile X mental retardation is caused by silencing of the fragile X mental retardation gene (Fmr1). This gene encodes a protein, fragile X mental retardation protein (FMRP), which plays a multifunctional role in protein synthesis and neuronal development (Bagni & Greenough 2005). FMRP binds to mRNAs and is involved in repressing their translation while transporting them to distal sites in cells. In neurons, upon intense synaptic stimulation, FMRP is thought to dissociate from its target mRNA leading to a derepression of translation (Bassell & Warren 2008). Synaptic synthesis of new proteins plays a key role in initiation and maintenance of plasticity and all evidence indicates that FMRP plays a crucial role in this process (Bassell & Warren 2008). Two forms of synaptic plasticity are altered in several

brain regions in the Fmr1-knockout mouse, a model of FxS: long-term depression is enhanced (Bear *et al*. 2004) and LTP is absent in some, but not all, brain regions (Li *et al*. 2002; Larson *et al*. 2005; Wilson & Cox 2007; Hu *et al*. 2008). The long-standing existence of this mouse model for FxS (The Dutch-Belgian Fragile X Consortium 1994), coupled with interest in the role of translation regulation in synaptic plasticity (Kelleher *et al*. 2004) and the high prevalence of FxS (Turner *et al*. 1996), has led to an extraordinarily in-depth understanding of the role of FMRP in synaptic plasticity.

One of us, TJP, conducted a detailed study of altered nociception in the mouse model of FxS (Price *et al*. 2007). While these mice had normal acute pain thresholds to mechanical and thermal stimuli, they showed a marked reduction in assays designed to assess amplification in pain pathways. One of the strongest phenotypes of the FMRP-knockout mouse was a lack of wind-up in dorsal horn neurons. As mentioned above, wind-up is a major mechanism of short-term plasticity in pain pathways and its near absence in this mouse model suggests that a severe deficit in spinal pain processing is present in this disease. In fact, not only did we observe a lack of wind-up in these mice, but we also noted wind-down in several preparations, indicating that there may be a loss of synaptic responsiveness with repetitive stimulation of nociceptors in the absence of FMRP. In addition to this deficit in wind-up, longer-term forms of pain plasticity were also lacking in these mice. These included a long delay (3 weeks in Fmr1-knockout mice vs. immediate sensitisation in wild-type animals) in the development of neuropathic pain after peripheral nerve injury and a lack of metabotropic glutamate receptor 1/5 (mGluR1/5)-mediated nociceptive sensitisation. Because FMRP is strongly expressed in neurons of the pain pathway (Price *et al*. 2006) and translation regulation is known to play a key role in pain amplification processes (Price & Geranton 2009; Melemedjian *et al*. 2010; Asiedu *et al*. 2011), these findings are likely directly linked to FMRP-mediated control of nociceptive plasticity and not associated with other behavioural deficits present in this mouse model of the human disorder.

In contrast to Rett syndrome, studies directly assessing pain thresholds in FxS have not been conducted. Based on studies in the preclinical model, we would not anticipate changes in acute pain thresholds in FxS, but rather that pain amplification would be impaired. In keeping with this hypothesis, the fragile X premutation tremor/ataxia syndrome (FXTAS) does provide some interesting potential insight into this hypothesis. FXTAS, unlike the full mutation that leads to FxS (Hagerman & Hagerman 2002), does not repress FMRP expression but rather leads to an increase in FMRP mRNA expression (Hessl *et al*. 2005). Humans with FXTAS frequently develop peripheral neuropathies that have a high frequency of associated pain (Berry-Kravis *et al*. 2007; Brega *et al*. 2009). Moreover, the incidence of the functional pain amplification disorder, fibromyalgia, is significantly increased in patients with FXTAS (Coffey *et al*. 2008). Taken together, the preclinical and clinical evidence strongly suggests a major role for the Fmr1 gene in pain amplification.

From preclinical evidence to self-injurious behaviour

While the available evidence clearly points to deficits in either acute pain perception or pain amplification in the absence of MeCP2 or FMRP, a link between these proteins, their disorders and SIB has yet to be established. One limitation is that mouse models of Rett syndrome and FxS do not demonstrate SIB or even repetitive grooming behaviours which may be interpreted as SIB in mice (Silverman *et al*. 2010). On the other hand, we feel that the preclinical evidence detailed above creates a useful framework through which testable hypotheses can be made. It is feasible that decreased pain thresholds and/or a lack of amplification underlie the persistence of SIB. In such a model, initiation of nociceptor discharge by SIB would be expected to lead to both wind-up and LTP in pain pathways based on the intensity and duration of SIB bouts (Newell *et al*. 2002a). This would lead to an

amplification of pain signalling initiating a protective reflex, an evolutionarily conserved process that would be self-limiting. In contrast, in the absence of such amplification mechanisms, as is likely in Rett syndrome and demonstrated in a preclinical model of FxS, these protective reflex mechanisms might fail to engage leading to the persistence of SIB either within bout or as a consistent stereotypy. While this model would have to be tested in human subjects, there are several methods that have been employed in other settings that could be utilised. LTP can be induced in human pain pathways through stimulation of dermatomes with electrical current. This procedure leads to brief pain and a longer lasting primary hyperalgesia and secondary allodynia, on the order of 30 min (Klein *et al*. 2004, 2008; Lang *et al*. 2007). This procedure, coupled with the advent of a validated quantitative sensory testing score for non-verbal adults with neurodevelopmental disorders (Symons *et al*. 2010), could be utilised to test for an absence of perceptual correlates of LTP in Rett syndrome and FxS. Another potential approach could involve functional magnetic resonance imaging (fMRI). The LTP protocol mentioned above would be expected to stimulate activity in the so-called pain axis (Apkarian *et al*. 2005) in control subjects, while activation of these brain centres in Rett syndrome or FxS would be attenuated. Less invasive procedures, such as a brief noxious pinch or wind-up protocols, may be capable of revealing major differences in engagement of brain centres involved in pain processing in these syndromes. Furthermore, the utilisation of these techniques to compare individuals with these or similar disorders that self-injure versus those that do not may reveal additional differences in pain processing within syndrome populations that would be informative in understanding the potential connection between decreased pain amplification mechanisms and SIB. Finally, and most simply, SIB should lead to the presence of both hyperalgesia and secondary allodynia directly following its termination if pain amplification pathways are intact. We would hypothesise that such effects would not be observed in individuals with Rett syndrome, FxS or other similar disorders. This hypothesis is immediately testable in many observational settings through the use of non-verbal pain inventories and quantitative sensory testing (Symons *et al*. 2010). While we do not deny that these approaches may present major technical (fMRI) and complex ethical hurdles, gaining a further understanding of the role of pain amplification deficits in SIB may lead to new treatment approaches and a better grasp on the neurobiological underpinnings of the problem.

There is ongoing discussion in the ID community regarding reduced pain sensation and ID patients. Several studies have indicated that baseline pain thresholds are normal in ID patients (Hennequin *et al*. 2000; Defrin *et al*. 2004). To the best of our knowledge, all studies in the ID population address baseline pain thresholds and not pain amplification. A key aspect of the proposal discussed herein is that pain amplification may be dysregulated in certain ID patients, even if baseline pain thresholds are normal. In addition, very few published reports on pain sensation in ID patients specify the type of ID under investigation. Differences in pain sensation among ID syndromes could explain conflicting interpretations in the literature. For example, it is possible that patients with Rett syndrome have reduced pain sensation as observed in the Australian study (Downs *et al*. 2010), while those with Down syndrome have normal pain thresholds, as demonstrated by Defrin *et al*. (2004). It is important to note that the Australian study was a review of parental recall regarding pain thresholds in Rett patients (Downs *et al*. 2010), while the study by Defrin *et al*. employed formal sensory threshold testing (Defrin *et al*. 2004); however, including ID type in future publications assessing pain and SIB would shed light on conflicting data from studies that have pooled all patients with severe ID into a single group. Also, we wish to acknowledge the risk in speculating about capacity to experience pain in this sensitive population that often cannot adequately express their needs or may have cortical deficits that fundamentally change the pain experience. Any clinical study addressing pain amplification should be thoroughly reviewed for ethical integrity and measures should be standardised to avoid *a priori* bias of investigators. Investigators must take great care in interpreting and reporting

their data because many caregivers believe that children with severe ID do not experience pain normally and these beliefs may influence the quality of care provided (Breau *et al*. 2003b). It is possible that pain signalling is defective in a subset of ID patients and identifying those individuals most likely to have altered pain processing may allow for tailored treatment for SIB.

Self-injury as a coping mechanism for pain in patients with intellectual disability

Several groups have proposed that SIB may serve as a coping mechanism for severe pain because self-injury should activate descending inhibitory mechanisms in the pain pathway (Bosch *et al*. 1997; Breau *et al*. 2003a; Symons & Danov 2005). In a cohort of ID children with and without various types of chronic pain and exhibiting varying degrees of SIB, Breau *et al*. (2003a) found children with chronic pain tended to engage in SIB less frequently, injure a smaller body area and target the site where pain originated, while those patients without identifiable pain who engaged in SIB tended to self-injure more frequently and in a diffuse pattern. These findings raise the possibility that there are qualitatively different forms of SIB initiated and propagated for different reasons (Breau *et al*. 2003a). Compulsive SIB directed towards painful areas also can occur in children (Symons & Danov 2005) and adults (Mailis 1996) with intact mental status suffering from neuropathic pain and treatment of the underlying pain condition resolves SIB in many cases (Mailis 1996). Thus, the occurrence of SIB as a coping mechanism for chronic pain may not be limited to the ID population. Multiple factors contribute to initiation, nature and perpetuation of SIB, thus coping with pain should be considered as a motive on an individual basis. It may be beneficial to include type of ID syndrome and nature of self-injury (e.g. diffuse vs. targeted and which sites) in future studies to identify factors indicative of SIB as a coping mechanism for pain.

Diffuse noxious inhibitory control

In cases where SIB is associated with chronic pain, self-injury may be working in a similar fashion to the counter-irritation principle as proposed by several groups in the 1980s (Le Bars *et al*. 1979a; Pertovaara *et al*. 1982; Willer *et al*. 1982). Based on the intensity and duration of self-injury exhibited by ID patients (Newell *et al*. 2002b), this behavior should engage reflexive diffuse noxious inhibitory control (DNIC). DNIC was first described as an experimental paradigm in which a painful conditioning stimulus increases hetero- or homotypic pain thresholds in distal locations in rats (Le Bars *et al*. 1979a) and humans (Willer *et al*. 1984) as measured by withdrawal reflexes. In the healthy population, DNIC is activated by noxious stimuli very close to the detection threshold. However, if pain processing is attenuated in ID patients, the stimulus required to engage DNIC may be much higher than what is observed in normal individuals. DNIC is a result of inhibitory signalling derived from the brain and brainstem because spinalised animals [animals with brain/spinal cord connections disrupted (Le Bars *et al*. 1979b)] and humans with lesions that interrupt communication between higher structures and the spinal cord (Roby-Brami *et al*. 1987; De Broucker *et al*. 1990) do not exhibit altered reflex withdrawal thresholds under conditions that stimulate DNIC in intact animals or individuals (Le Bars *et al*. 1979a). DNIC depends in part upon the endogenous opioid system as a low dose of the μ-opioid receptor antagonist naloxone that does not affect reflexes in the absence of conditioning stimulus (Boureau *et al*. 1978; Willer *et al*. 1990) completely blocks DNIC in rats (Le Bars *et al*. 1981) and humans (Willer *et al*. 1990). A meta-analysis has indicated that the μ-opioid receptor antagonist naltrexone improves SIB in 50–80% of ID patients (Symons *et al*. 2004). This study supports the hypothesis that engaging the endogenous opioid system is a motivating factor

for some ID patients, consistent with a scenario in which ID patients activate DNIC through SIB to cope with pain.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is one of the best studied causes for SIB in ID patients with chronic pain. GERD causes severe visceral pain and occurs with greater frequency among children with different types of severe ID compared to mentally healthy children (Sondheimer & Morris 1979; Cates *et al*. 1989; Spitz *et al*. 1993; Motil *et al*. 1999; Gössler *et al*. 2007). Multiple studies have linked the presence of GERD with SIB in ID children and in some cases GERD treatment reduced the incidence of SIB (Bosch *et al*. 1997; Luzzani *et al*. 2003). Swender *et al*. were among the first to specifically test the *a priori* hypothesis that GERD may be causally related to handmouthing in Rett patients. This group also identified a correlation between GERD and SIB in ID children; however, they found that GERD treatment did not alter behaviour and concluded that SIB may take on secondary functions in this population (Swender *et al*. 2006). Nevertheless, pharmacological intervention to alleviate pain due to GERD may be an important component of treatment of SIB, and GERD status should be assessed in susceptible patients.

Mechanistic work (Mittal *et al*. 1995; Young *et al*. 2007) has revealed a promising pharmacological target for GERD treatment. GERD is caused by transient relaxation of the lower oesophageal sphincter (LES) due to poor neural control (Holloway & Dent 1990; Dent 1998). The vagus nerve senses stomach distension after eating, triggering LES relaxation (Mittal *et al*. 1995). Inhibiting the metabotropic glutamate receptor 5 (mGluR5) decreases the sensitivity of vagal mechanoreceptors reducing frequency of LES relaxations (Young *et al*. 2007). Treatment with the mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP) reduces transient LES relaxations by up to 90% in animal models (Frisby *et al*. 2005; Jensen *et al*. 2005) and the negative allosteric modulator of mGluR5, ADX10059 has demonstrated efficacy for GERD treatment in phase I (Keywood *et al*. 2009; Zerbib *et al*. 2010) and phase II (Zerbib *et al*. 2011) clinical trials in otherwise healthy individuals. Excessive mGluR5 signalling is implicated in the pathology of FxS and the inhibitors under investigation in clinical studies for FxS have been well tolerated in this population (Berry-Kravis *et al*. 2009; Jacquemont *et al*. 2011). These trials were not designed to test the effect of mGluR5 inhibition on GERD-associated visceral pain and SIB. Including these measures as primary endpoints in subsequent trials will provide needed evidence to test the hypothesis that SIB might be managed through better GERD control in the ID population.

Ongoing pain should be considered as a potential driving factor for SIB in ID patients, but further work is required to assess the relationship between self-injury, chronic pain and DNIC. Discovery of mechanisms linking self-injury to pain and DNIC may reveal additional pharmacological targets, similar to the mGluR5 inhibitors mentioned above. It is worth noting that pain treatment would be useful only in the subset of ID patients that initiate self-injury in response to pain, and that each patient should be evaluated individually for the contribution of pain to SIB. Furthermore, if SIB is initiated due to pain but adopts secondary functions, pain management may improve behaviour, but resolution of SIB will likely require a multipronged approach. Improved methodologies for pain assessment in children with severe ID (Symons *et al*. 2010) can facilitate the study of the relationship between pain and self-injury. Further clinical studies addressing the role of pain in self-injury initiation and persistence should lead to improved strategies for controlling SIB.

Concluding remarks

Pain and pain amplification are evolutionarily conserved phenomena critical for survival but can be dysregulated in some disease states (Woolf 2010). The extent of pain experienced by

an individual depends upon spinal gating (Melzack & Wall 1965; Woolf & Salter 2000), which is in turn regulated by higher centres in the brainstem and brain (Ossipov *et al*. 2010). Preclinical and some clinical studies indicate that pain amplification may be diminished in certain syndromes that cause severe ID such as FxS (Price *et al*. 2007) and Rett syndrome (Downs *et al*. 2010). There is conflicting evidence regarding pain thresholds in the ID population with Rett patients appearing to have decreased sensitivity, albeit as assessed by parental recall and requiring further threshold testing (Downs *et al*. 2010) and Down syndrome patients having normal or possibly enhanced pain thresholds (Defrin *et al*. 2004). This could reflect differences in pain processing among ID syndromes as individual molecular defects leading to clinical features of each disease may impact the nociceptive system differently. Furthermore, we are unaware of any published clinical studies evaluating aberrant pain amplification in ID patients. Baseline thresholds may remain normal in certain ID patients, but without effective pain amplification, pain due to self-injury may not be sufficient to deter SIB. Studies evaluating pain amplification in ID patients have the potential to reveal the extent to which pain amplification may be dysregulated in ID patients and linking altered pain processing to SIB may reveal new pharmacological targets for this difficult behaviour (e.g. mGluR5 antagonists). Some existing clinical data support the hypothesis that SIB may be a coping mechanism for certain ID patients dealing with chronic pain. In this paradigm, self-injury activates DNIC, a centrally mediated, opioid-dependent dampening of spinal pain processing that decreases the severity of pain sensation. Identifying ID patients suffering from chronic pain and incorporating pain management into their treatment may improve therapeutic outcomes for SIB. Evaluating pain amplification and/or processing as well as chronic pain status in clinical studies of ID patients may provide insight into mechanisms driving SIB in this population.

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