Pathophysiology of GER

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Abstract

The pathophysiology of gastroesophageal reflux disease (GERD) is multifactorial. It usually involves the function of the lower esophageal sphincter and esophageal peristalsis, as well as mucosal changes that result from the presence of the refluxate, and their consequences on pain perception. Transient lower esophageal sphincter relaxation is the most common event associated with reflux, and esophageal peristalsis is necessary to clear the esophagus from the refluxate. Abnormal permeability of the esophageal mucosa can result from reflux, and this may result in increased mucosal permeability that may lead to esophageal damage and pain sensitization. There are specific pathologic conditions that affect the mechanisms responsible for the prevention of GERD, so it is more common in certain populations.

Keywords

Gastroesophageal reflux disease · Transient lower esophageal sphincter relaxations (TLSERS) · Mucosal integrity · Intracellular spaces · Pain sensitization

Gastroesophageal reflux (GER) is a normal physiologic event that occurs multiple times a day, but that frequently evolves into a pathologic entity (gastroesophageal reflux disease (GERD)), when it becomes troublesome and symptomatic or is associated with esophageal damage or extraesophageal problems [1].

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GER is physiologic and more common in infants, and factors that contribute to the more frequent physiologic reflux in the infant include a combination of large fluid intake, a supine position that predisposes to a common immersion of the gastroesophageal junction, compounded by a small esophageal capacity to hold fluids [1–3].

The pathophysiology of GERD is multifactorial [4]. It is related on one hand to lower esophageal sphincter (LES) function and anatomy, and on the other to esophageal events that lead to reflux clearance, mucosal damage, and perception of the refluxate [4, 5]. The LES acts as a barrier to reflux, and the esophageal mechanisms include either (a) peristaltic waves that prevent the reflux from reaching very high toward the mouth and provide clearance of the refluxate toward the stomach and (b) esophageal mucosa and other physiologic events that prevent damage from the refluxate, and contribute to the perception and pain that is associated with reflux [2, 4–6].

In this chapter, we will review the different mechanisms that contribute to the pathophysiology of GERD in the pediatric population.

LES Function

An important part of study of the pathophysiology of GERD in children has focused on understanding the role that the LES plays [4, 7]. Conceptually reflux occurs when the LES pressure is lower than the intragastric pressure, which can occur either because the LES pressure is low, because of inappropriate relaxations or because the abdominal pressure is higher than the LES pressure.

The LES is primarily innervated by the parasympathetic system via the vagus nerve. At basal state, it remains "closed" in tonic contraction because of the excitatory cholinergic pathway. LES relaxation or "opening" occurs as a reflex response to swallowing, pharyngeal stimulation, esophageal distention (spontaneous or provoked), gastric distention, and abdominal strain via the inhibitory nitrergic pathway [6, 8]. It has now been shown in multiple studies that contrary to the initial hypothesis, in the vast majority of children, including premature infants, GER is not related to a decreased tone of the LES [2, 5–10]. The central motor control of the LES is fully developed during the intrauterine stage, although there may be some maturation that occurs in premature babies, until they become full term. All infants (PMA 33–38 weeks) had a high-pressure zone at the LES with a mean pressure of 20.5_1.7 mmHg and swallow-induced esophageal body motility showed a normal peristaltic progression [2, 8, 10].

Gastroesophageal reflux can occur via four main mechanisms. Transient Lower Esophageal Sphincter Relaxations (TLSERs), low LES pressure, swallow-associated LES relaxations, and straining during periods with low LES pressure [4, 8]. It is now known that the predominant mechanism through TLSERs (Fig. 2.1) [2, 4–8] which are relaxations of the LES that are not preceded by swallowing, and they facilitate the retrograde passage of gastric contents into the esophagus [8]. High-resolution manometry is the new gold standard to detect TLSERs. Using HRM,

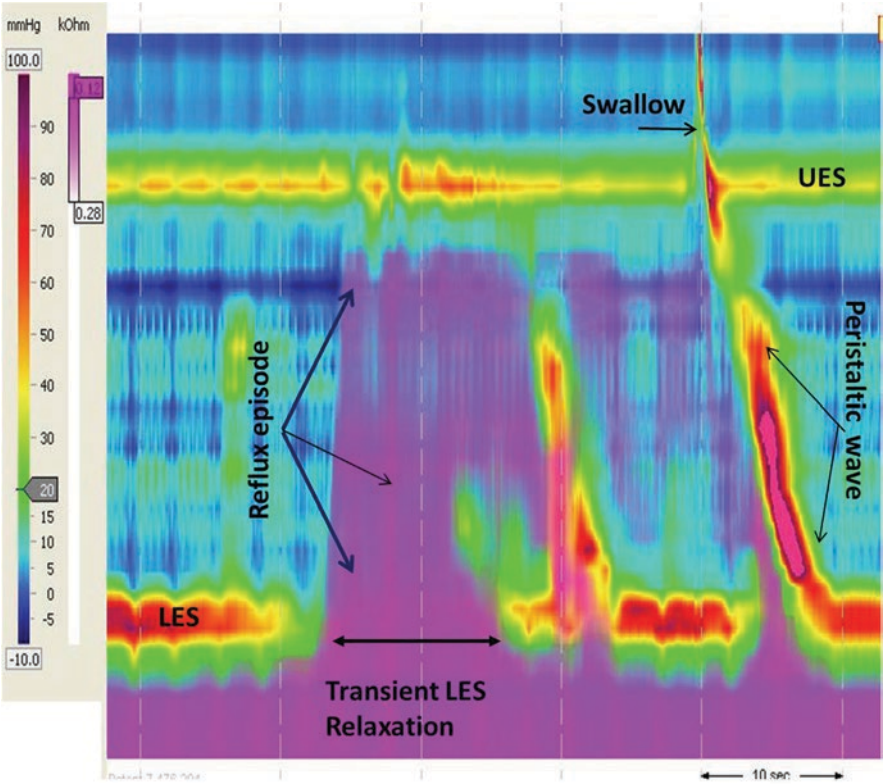

Fig. 2.1 Transient lower esophageal sphincter relaxation (TLSER) with a reflux event. The figure shows a tracing from a high-resolution esophageal manometry with impedance during an episode of gastroesophageal reflux (pink color). The episode is occurring after there is a relaxation of the lower esophageal sphincter that is not associated with swallowing. The reflux episode is followed by a normal swallow that clears the refluxate

TLESR might be defined as LES relaxation occurring in absence of swallowing, lasting more than 10 s and associated with inhibition of the crural diaphragm [11, 12] (Fig. 2.1). Gastric distension is a potent stimulus for TLESR, via vago-vagal pathways [13]. In infants, more TLESRs were triggered when feedings are administered in the right lower position, as compared with the left lateral position [8, 13].

Not all TLSERs are associated with reflux events, and when comparing controls with patients with gastroesophageal reflux disease (GERD) TLESRs do not occur more often in patients with GERD [4, 8, 14, 15]. However, in patients with GERD the TLSERs are more likely to be associated with reflux as compared to healthy controls [16, 17]. The mechanism behind this phenomenon remains largely unknown. The frequency TLSERs that are associated with more reflux is higher when the osmolarity and volume of the meals increases [15]. Most reflux occurs in the postprandial period, although nocturnal reflux has been associated with an increased severity.

An interesting observation has been that even though TLSERs explain why reflux is more frequent in the postprandial period they do not explain why the refluxate is more acidic. The paradox of acid reflux occurring at a time when the intragastric environment is least acidic due to the buffering effect of the meal was unraveled by the discovery of the acid pocket [18]. The acid pocket forms due to the buffering effect of food within the stomach. The acidity falls within the main stomach body where the mixing of food and gastric juice is at its greatest. The proximal stomach relaxes after a meal and acts as a reservoir for food. Acid in this area will therefore escape the buffering effect of the meal [18]. The lack of mixing will also allow gastric juice to pool and form a layer of acid on top of the gastric contents. Therefore, increase reflux during a TLSER may be related to the acid pocket, that reaches more proximally in patients with GERD than in healthy people thereby providing a reservoir of unbuffered acid and gastric contents that will probably reflux whenever the LES fails [18, 19].

The esophageal wall stiffness and the distensibility of the GEJ have been recently measured with the functional luminal imaging probe (FLIP), and studies have shown that there is no correlation between the measurements obtained with the FLIP and reflux monitoring [20].

Delayed gastric emptying has been suggested as another factor that can increase TLSERs and reflux [21], although the evidence that there is an association is controversial and most studies in children do not show a correlation [2, 22].

Exercise has been associated with an increase in the percentage of transient lower esophageal sphincter relaxations (TLESRs) that resulted in reflux significantly increased during exercise and all but one reflux episode occurred during TLESRs [23]. Ingestion of medications or other substances (nonsteroidals, antibtiotics, alcohol), and ingested nutrients (fatty and spicy foods, tomato-based sauces), can also lead to increased TLSERs.

Other LES related mechanisms that have been postulated include a failure in young children of the LES to respond to a sudden increase in intra-abdominal pressure, such as during crying, as well as reductions in intrathoracic pressures, as in bronchopulmonary disease [24], and in a very small percentage of patients that usually have underlying conditions that affect the tone of the smooth muscle, like scleroderma, congenital malformations or other smooth muscle myopathies the basal tone of the LES is low [25].

Other Structural Abnormalities

The antireflux barrier is not only comprised of the LES [4, 5]. The esophagogastric junction (EGJ) functions as an antireflux barrier and consists of the smooth muscle of the LES which is surrounded by oblique gastric fibers. These are anchored to the striated muscle of the crural diaphragm by the phrenoesophageal ligament [4]. The lower esophageal sphincter and the crural diaphragm form a high-pressure zone that functions as an antireflux barrier. Their synergistic function is supported by the angle of His and gastroesophageal flap valve [5]. Therefore, there are other structural and physiologic antireflux mechanisms at the gastroesophageal junction, like

the diaphragm and the phrenoesophageal ligament. In children with reflux disease, the morphology of the LES and cardia may be distorted and demonstrate shortening of the intra-abdominal part of the esophagus, a rounded gastroesophageal junction, and obliteration of the angle of His when assessed by ultrasonography [4, 5, 26]. In patients with a hiatal hernia, the antireflux barrier is compromised as there is dissociation of the internal LES sphincter from the external diaphragmatic crura which leads to sphincter weakening [5, 27]. There is also an increased number of TLSERs [28]. However, in limited pediatric studies it has been shown there was no difference in the prevalence of GER comparing children with or without a hiatal hernia [5, 9].

The body position has an effect on reflux events [5, 8, 29]. Prone and left lateral position resulted in lower acid and nonacid reflux indexes. In addition, studies using esophageal manometry techniques showed an increased number of TLESRs and GER episodes in infants lying in the right-side lateral position [8]. In healthy preterm infants, the right lateral position shows the highest number of liquid reflux events but as it promotes gastric emptying. Therefore, it is still recommended to place infants in the right lateral position for the first postprandial hour and thereafter in the left later to enhance gastric venting and obliterate reflux events [29].

Esophageal Mechanisms

Esophageal Peristalsis

There are some esophageal mechanisms that also participate in the pathophysiology of GERD. These include insufficient clearance, buffering of the refluxate, mucosal abnormalities, and impaired neural protective aerodigestive reflexes [2, 4, 5, 8].

Esophageal clearance of refluxate is directly related to the presence of normal esophageal motility [4, 8, 30]. A normal motility is needed to avoid the possibility of the reflux going high toward the mouth, and to provide a rapid clearance once the refluxate is present [5, 6, 8, 30]. Swallow-induced peristalsis is fully developed at the gestational age of 26 weeks while secondary peristalsis has been described as early as 32 weeks gestation [8]. Postnatal maturation of the peristaltic propagation leads to improved bolus propulsion and transit velocity and continues throughout the infant/toddlers years till childhood [5, 8].

There has been some controversy about whether impaired esophageal motility in patients with severe reflux disease is a primary problem directly contributing to the pathophysiology of the disease or a consequence of the reflux [8, 9, 30, 31]. Theoretically, esophageal mucosal inflammation may affect nerves and muscles that alter LES function and esophageal body motility. A vicious cycle of inflammation and impaired motility may cause progressive disease [9, 31]. It has been shown that in patients with GERD there may be subtle alterations in esophageal peristalsis [9, 30], although most patients have normal esophageal motility. These mild abnormalities have been found in some studies not to be related to the presence of esophagitis, suggesting there may be an underlying motility disturbance in children with GER [9, 31].

In children with GERD, there is a higher incidence of nonspecific esophageal motility defects during primary peristalsis and their prevalence increases with disease severity [5]. Children with erosive disease present with a 30–50% decrease in pressure wave amplitude indicating impairment of the esophageal contractile vigor [32]. Clearing efficacy is achieved with primary peristalsis in 70.86% of pediatric nonerosive reflux disease (NERD) versus 52.08% of pediatric GERD and with secondary peristalsis in 45.45% of pediatric NERD and 20% of pediatric [32]. Similar abnormalities in secondary peristalsis in GERD patients have been described in adults [30]. These abnormalities are increasingly recognized as important in the genesis of delayed refluxate clearance [30], as they contribute to the maintenance of an empty esophagus by clearing refluxed gastric contents or residual food bolus after a failed primary peristalsis or after a reflux event.

In patients with severe motility dysfunction, as is observed in children with esophageal atresia [33] or patients with scleroderma [25], the abnormal motility predisposes to delayed clearance and more esophagitis.

Esophageal chemical clearance is aided by saliva. Saliva contains bicarbonate, which buffers acid, and growth factors, such as epidermal growth factor, which promotes mucosal repair and defenses [4]. Esophageal clearance with saliva has recently been measured indirectly with Impedance monitoring by using the postreflux swallow-induced peristaltic wave (PSPW) [34], which is a clearing wave originating in the upper esophagus that reaches the lower esophagus, and occurs within 30 s after the end of a reflux episode. It has been suggested that it reflects salivary clearance of a reflux episode. The PSPW has been shown to separate erosive reflux disease patients, from nonerosive reflux patients, and non-GERD patients including functional heartburn [34, 35]. These suggest that abnormal chemical esophageal clearance may play a role in the pathogenesis of GERD.

Esophageal Mucosa Defense

The esophageal mucosa has defense mechanisms that are designed to protect it from excessive acid exposure. The esophageal lumen is protected from transient acid exposure by the buffering action of bicarbonate coming from saliva and esophageal submucosal glands, as well as the clearing action of gravity and esophageal peristalsis [4, 5]. Mucosal defense mechanisms may be overcome by prolonged exposure of the esophageal mucosa to a pH <4 that may lead to severe and complicated esophagitis. Acid is not the only component of the refluxate, as gastric contents also include pepsin, and even bile, or pancreatic and duodenal enzymes.

It has been shown that the combination of acid and proteolytic enzymes causes more esophageal damage than acid alone. Decades-old experiments performed on cats showed pouring hydrochloric acid with a pH 1.3–2.0 into the esophagus for 1 h did not cause acute esophagitis. However, solutions of the same pH that also contained pepsin led to the development of esophageal erosions. However, studies show that the levels of pepsin in gastric juice and the maximum output of pepsin are not different in patients with or without esophagitis [36]. Generally, the intact

epithelium is protected from pepsin-mediated damage if the refluxing pH is greater than 5. The role that bile plays is also controversial. The presence of duodenogastroesophageal reflux alone as measured by bilirubin content did not produce esophagitis in partial gastrectomy patients. Patients with both acid and duodenal content in the esophagus had a high frequency (67%) of esophagitis and duodenogastric reflux is more common in GERD patients with stricture or Barrett's esophagus. Therefore, as with pepsin, the presence of acid in the gastroesophageal refluxate is required for the duodenal content to have its potential deleterious effect on the production of esophagitis. Recent experimental evidence suggests that bile may indeed have a role [37, 38]. Recent animal studies have shown that bile produces dilatation of the intracellular spaces in esophageal epithelium [37–39].

Mucosal Integrity

Problems in mucosal integrity have been identified histologically by measuring intercellular space [40], in vitro [41] by measuring permeability and electrical resistance, and by using baseline esophageal impedance values in vivo [5, 42].

The impaired mucosal integrity was initially suggested by histological findings that showed dilated esophageal intercellular spaces (ISD) in patients with GERD [5]. Increased ISD have been shown to represent an early morphological marker of reflux injury in the esophageal epithelium [40, 41, 43, 44]. Changes have been shown to be independent of visible erosions, and have been shown both in erosive (ERD) and nonerosive reflux disease (NERD) [40–44]. Experimental models initially showed that DIS dilation occurred as a consequence of acid peptic injury to the esophageal epithelial cells [37]. Recently it has been shown that continuous exposure of the esophageal mucosa to both acidic and weakly acidic solutions can impair mucosal integrity inducing identical morphological changes to those observed after perfusion with acid solutions [37]. Abnormal DIS in patients with erosive esophagitis has been shown to normalize following antisecretory therapy [41].

In vitro measurements of mucosal integrity using different methodologies have shown abnormalities in animal models, and patients with GERD [5, 41]. With the use of *Ussing chambers, to evaluate* transepithelial mucosal resistance and permeability it has been shown there is increased permeability and decreased mucosal resistance in patients with GERD. Those abnormalities correlate to the degree of acid exposure and exposure to other gastric contents [37, 39], and are reversible with successful therapy [41].

Baseline esophageal impedance values have been correlated with in vitro measurement of mucosal integrity using a Ussing Chamber, so they provide a validated tool [42]. Studies in experimental animals have shown that in vivo esophageal perfusion with an acid solution decreased the transepithelial resistance and increased the paracellular permeability in vitro, which were in turn associated with dilated ISD, supporting the hypothesis that measurement of esophageal transepithelial epithelial resistance in vitro might provide useful information on the esophageal

mucosal integrity. Baseline impedance values in patients with GERD are low, while they are high in normal healthy volunteers [45, 46]. Baseline impedance values correlate with esophageal acid exposure time, and low impedance values have been shown in patients with severe esophagitis, Barrett's, and patients with nonerosive reflux disease [5, 42, 44–46]. More importantly previous findings have shown that the baseline impedance levels increase in response to PPI treatment [40, 41, 43, 44]. Adult patients with NERD have lower baseline mucosal impedance than controls and patients with functional heartburn (FH) while greater sensitivity to acid is observed in patients with lower baseline impedance [5]. In pediatrics, baseline impedance shows a negative association with acid exposure and is predictive of erosive esophagitis [45, 46].

The relationship between mucosal impedance and DIS is not so clear, and recent pediatric studies have shown that the distal baseline impedance in children with GERD did not correlate with the degree of ISD [44], suggesting they may be measuring different aspects of esophageal function.

Sensation

Not all patients with GERD have symptoms, and many patients with GERD symptoms do not have excessive acid exposure [4, 5]. The mechanisms that lead to the perception of the refluxate or to symptoms are not well understood, but multiple factors may influence them. In neonates the strongest stimulus for symptom generation was volume and this was independent of GERD severity as expressed by means of esophageal acid exposure time. Water and apple juice, stimulating osmoreceptors and chemoreceptors, respectively, produced more cardiorespiratory symptoms compared with air, stimulating mechanoreceptors [47]. No similar studies are available in older children.

Sensory abnormalities have become more important in recent years with the recognition of reflux-related entities that are mostly sensory in nature, like functional heartburn, or reflux hypersensitivity [4, 5, 41, 44, 48–50]. It has become evident that an important underlying mechanism in patients with esophageal symptoms is the presence of esophageal hypersensitivity [4, 5, 41, 44, 48, 50].

Esophageal sensitivity is determined by both peripheral and central mechanisms [4, 5]. It has been hypothesized that this enhanced esophageal sensitivity for reflux in GERD patients is caused by the impaired mucosal integrity that has been described in GERD [41, 43, 44]. It is important to note that in recent studies both in children [40, 42] and adults [41] it was shown that there is no correlation between reflux severity or the reversal of the mucosal changes after therapy, and the perception of symptoms, suggesting that the enhanced sensitivity to reflux episodes is not only explained by increased mucosal permeability [41]. It has been hypothesized that this impaired mucosal integrity enables the refluxed material to reach the sensory nerve endings through dilated intracellular spacing, activating chemosensitive nociceptors which in turn transmit signals via the spinal cord to the brain resulting in symptom perception, and pain sensitization [40–42]. Therefore, pain sensitization can occur both at peripheral and central levels.

Peripheral sensitization can occur after excessive stimulation of the peripheral receptors of the afferent nerve endings can lead to an upregulation of these receptors through the release of intracellular inflammatory mediators and thus lead to a reduced threshold of transduction [48, 50]. For example, the infusion of acid reduced the esophageal pain threshold in patients with noncardiac chest pain, and after acid infusion into the distal esophagus, pain thresholds in both acid-exposed distal esophagus and nonexposed proximal esophagus were reduced in patients and healthy controls [51].

Furthermore, the decreased pain threshold in patients with GERD-related noncardiac chest pain was increased after proton pump inhibitor (PPI) treatment [51].

It is also not clear if the distribution of mucosal nerve fibers differs when comparing patients with NERD or GERD. In a study of adults it was shown that proximal and distal esophageal mucosa of patients with NERD have more superficial afferent nerves compared with controls or patients with GERD, suggesting that acid hypersensitivity in patients with NERD might therefore be partially explained by the increased proximity of their afferent nerves to the esophageal lumen [52]. However, a recent study in children demonstrated that the mucosal innervation in children with NERD is similar to controls, with deep-lying nerve fibers both in the proximal and distal esophagus [53].

Various receptors have been found to be involved in peripheral sensitization, including the transient receptor vanilloid 1 (TRPV1) receptor, the TRPV4- and the TRPA1-receptor, the acid-sensitivity ion channels, and the purinergic (P2X) receptors [4, 5, 52, 54]. TRPV1-receptor expression is higher in the inflamed esophageal mucosa. It has been proposed that TRPV1 activation due to acid-induced inflammation results in the synthesis and release of substance P and calcitonin gene-related peptide from submucosal neurons and of platelet-activating factor by the epithelial cells [54], which are pro-inflammatory mediators thus promoting further inflammation which could lead to increased mucosal permeability and further peripheral sensitization [4, 5, 50].

Central mechanisms, attributed to altered processing of afferent signals from the esophagus, have also been implicated. Recent studies suggest that esophageal pain and heartburn perception in some patients with functional heartburn, or esophageal hypersensitivity may also be due to *central sensitization* [55]. Acid stimulation of the esophagus can sensitize the insula and cingulate cortex to subliminal and liminal non-painful mechanical stimulations [50, 55]. The suggested mechanism is that enhanced nociceptor input results in repetitive signaling cascades in the spinal dorsal horn neurons which subsequently lead to facilitated excitatory synaptic responses and depressed inhibition, resulting in amplified responses to both noxious and innocuous inputs [50, 55]. Interestingly, using fMRI it was found that the same stimulus was perceived more intensely during a negative emotional context and was associated with increased cortical activity in the anterior insula and the dorsal anterior cingulate gyri than during a neutral emotional context [56]. Moreover, it has been demonstrated that acid exposure in GERD patients leads to a more rapid and greater cerebral activity than in healthy controls [4, 5, 50].

This sensitization effect can be modulated by drug manipulation. In a controlled study of healthy subjects, citalopram, a selective serotonin reuptake inhibitor (SSRI) given intravenously, significantly increased sensory thresholds and prolonged the time for the perception of heartburn after acid infusion. In randomized trials, SSRIs were shown to be effective in the treatment of patients with hypersensitive esophagus [57].

Special Patient Groups

There are certain patient groups at increased risk of GERD and its complications, and they will be discussed in detail in their respective chapters. Overall, neurologic impairment, and cerebral palsy, in particular, are one of the most common conditions that predispose patients to severe GERD [4, 5, 8, 58, 59]. Several studies confirmed the high prevalence of reflux esophagitis and pathological pH monitoring in NI children [9, 58, 59]. Some chromosomal abnormalities, like Cornelia de Lange [60], are associated with severe GERD. Patients with certain congenital esophageal abnormalities, such as repaired esophageal atresia or congenital diaphragmatic hernia are also associated with an increased risk of GERD [5, 8, 61]. An increased prevalence of GERD and its complications has also been reported in patients with chronic pulmonary disease, including cystic fibrosis [62].

The association between GERD and obesity has also been reported and total and abdominal obesity are risk factors for the development of GERD in children. Large epidemiological studies have demonstrated that obesity is an important risk factor of GERD [63, 64]. Pathophysiological mechanism in obesity includes lower esophageal sphincter abnormalities, increased risk of hiatal hernia, and increased intragastric pressure [64].

Conclusion

The pathophysiology of gastroesophageal reflux disease (GERD) is multifactorial. It usually involves the function of the lower esophageal sphincter and esophageal peristalsis, as well as mucosal changes that result from the presence of the refluxate, and their consequences on pain perception. A better understanding of the different mechanisms will lead to better and more specific therapies.

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