The Possible Role of Gonadal Steroids and 5HT₃ Receptors in Encouraging Menses

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Abstract

Serotonin (5-HT) and serotonergic receptors are strategic participants in nociception. Traumatic injury to peripheral tissues which results in arachidonic acid, bradykinin and prostaglandin release, initiates vasodilation and extravasation of serotonin which then binds with 5-HT₃ receptors on pain afferents. This sequence has been shown to mediate inflammatory pain both peripherally and centrally and is exclusively excitatory.

More recently, Wetzel has shown that gonadal steroids bind to 5-HT₃ receptors non-competitively, blocking 5-HT₃ receptor sites. This action interrupts propagation of painful stimuli potentially resulting in peripheral inflammatory analgesia.

A review of the available literature was performed with the purpose of establishing the location and actions of 5-HT₃ receptors in inflammatory pain, discussing the antagonism of 5-HT₃ by gonadal steroids and outlining how early estrus might influence inflammatory pain. Of particular interest are the possible effects of elevated serum estrogen levels on 5-HT₃ functionality in human pain and the potential for employing 5-HT₃ selective drugs as a method of therapy.

5-HT₃ receptors are non-competitively bound by circulating gonadal steroids and conduction of peripheral inflammatory pain is reduced or interrupted. Circulating gonadal steroids may affect the potential for conduction of inflammatory pain, enhancing the opportunity for near typical menses.

Keywords: Serotonin; 5-HT₃ receptors; Gonadal steroids; Menses

Background

Serotonin (5-hydroxytryptamine, 5-HT) is an abundant neurotransmitter found predominantly in enteric gastrointestinal enterochromaffin cells and platelets but also in the central and peripheral nervous system neurons [1]. Serotonin (5-HT) receptors are classified into a complex of four families based upon molecular characteristics. Each family is further subdivided into fourteen subtypes. Of these subtypes, 5-HT₃ is exclusively a ligand gated ion channel [2] and therefore distinct from the predominance of 5-HT₁ subtypes which couple to various GTP-binding proteins [3]. The serotonergic system’s role in the processing of pain has been extensively delineated. Bulbospinal and supratentorial serotonergic pathways suppress spinal system’s role in the processing of pain has been extensively delineated.

Injection of 5-HT into peripheral tissue initiates tissue trauma and the release of arachidonic acid, prostaglandins, bradykinin and the interleukins (IL-1,2& 6) in a dose-dependent response of inflammation and pain [10]. The release of kinins precipitates vasodilation and the release extravascular circulatory components such as platelets and free blood-borne serotonin [11]. Platelets release further serotonin into the surrounding tissues activating 5-HT₃ receptors on free nerve endings which are apparently responsible for nociceptive effects and probably also the perpetuation of a delayed secondary inflammation [7,10,12]. Delineation of the role of peripheral 5-HT₃ receptors was provided by peripheral intraplantar injections of 5-HT, antagonists ICS 205-930 and MDL 72222 which produced dose-dependent anti-nociceptive effects against inflammatory pain [12].

Action of peripheral 5-HT₃ receptors

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Action of central 5-HT₃ receptors

The central 5-HT system is a major participant in analgesia.

Table 1: SHT Family of receptors

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<th>Receptor</th>
<th>Subunits</th>
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<tr>
<td>5-HT₁</td>
<td>A</td>
</tr>
<tr>
<td>5-HT₂</td>
<td>A</td>
</tr>
<tr>
<td>5-HT₃</td>
<td>A</td>
</tr>
<tr>
<td>5-HT₄</td>
<td>A</td>
</tr>
<tr>
<td>5-HT₅</td>
<td>A</td>
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Table 1: 5-HT Receptors.
Serotonergic fibers from the raphe nuclei contribute to the dorsolateral funiculus which innervate the superficial dorsal horn of the spinal cord [13]. 5-HT<sub>3</sub> receptors have been identified in the superficial laminae of the spinal dorsal horn [9,4]. Activation of these descending 5-HT pathways causes the release of serotonin at synaptic connections with both nociceptive afferents and interneurons within the cord to produce analgesia [12,14]. Administration of 5-HT<sub>3</sub> receptor antagonists blocked 5-HT<sub>3</sub>-induced analgesia and produced a moderate hyperalgesic response [15]. The reduction of dorsolateral funiculus antagonists suggested that 5-HT<sub>3</sub> receptors are involved with the expression of feed back, serotonergic pain modulation at the spinal level [16]. Further, Intraspinal administration of the 5-HT<sub>3</sub> receptor agonist, 2-methylserotonin produced significant dose-dependent analgesia against inflammatory and thermal pain, but not mechanical pain [17].

Published data supports that 5-HT<sub>3</sub> released from descending dorsolateral funiculus pathways binds to spinal gray dorsal horn interneuronal 5-HT<sub>3</sub> receptors, depolarizing them [18]. Interneuron depolarization releases GABA and opioids which inhibit primary and/or second-order nociceptive neurons [17].

Table 2: Location of 5-HT<sub>3</sub> receptors

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<tr>
<th>Antagonism of 5-HT&lt;sub&gt;3&lt;/sub&gt; receptors by gonadal steroids</th>
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Gonadal steroids probably combine allosterically with 5-HT<sub>3</sub> receptors at the receptor-membrane surface [19] (Table 2). The competition between serotonin and gonadal steroids to react with 5-HT<sub>3</sub> receptor sites has been repeatedly demonstrated therefore establishing gonadal steroids as serotonin antagonists and potentiating analgesia [19]. Specifically, 17-beta-estradiol, testosterone and progesterone have been shown to act on the surface of the cell membrane as non-competitive antagonists for 5-HT<sub>3</sub> receptors [20-22]. Further, ovarian hormones play a role in regulating 5-HT<sub>3</sub> receptor expression in stress-induced bowel disfunction [23]. Both the 5-HT<sub>3</sub> receptor channel and the voltage-gated sodium channel are steroid targets. This is compatible with a common mechanistic principle in steroid-induced inhibition of the two channels [19].

Methods

A search of the current and historical literature was conducted.

Results

Early estrus influence on inflammatory pain

Many studies have suggested that a gender difference exists in the processing of painful stimuli in both humans and rats [24-27]. Further, several studies conclude that pain processing is estrus cycle stage dependant in rats [23,28]. 5-HT<sub>3</sub> receptors have been shown to mediate inflammatory pain both [1] peripherally, by depolarizing C-fibers which terminate in the dorsal horn and [2] in the spinal cord dorsal horn hyperpolarizing GABA and opioidergic interneurons which terminate on ascending secondary pain afferent (spinothalamic) neurons [21]. As previously stated, 5-HT<sub>3</sub> receptors are non-competitively antagonized by gonadal steroids [27,29].

Discussion

During the initial fourteen days of the female menstrual cycle estrogen levels rise in response to follicle stimulating hormone (FSH) effects on ovarian follicular cells. Though 70% of circulating estrogens are bound to sex steroid-binding globulin and 25% to plasma albumin, free estrogens are highest on the thirteenth day of menstrus [30]. With circulating estrogen levels high, making it more available for binding with 5-HT<sub>3</sub> receptors, it seems logical that females would be less responsive to inflammatory pain during that period and particularly at ovulation as a result of 5-HT<sub>3</sub> receptor competition as it has been shown in mice [31]. Circulating progesterone levels, in response to luteinizing hormone (LH) increase from day fourteen until approximately day twenty one, maintaining the potential for some level of continued inflammatory pain analgesia. However, there exists an obvious need for further investigation into the effects of gonadal steroids on pain resulting from tissue inflammation.

Conclusions

Competition between serotonin and gonadal steroids for the 5-HT<sub>3</sub> receptor site reduces the propagation of peripheral inflammatory nociception during periods of increased circulating gonadal steroids. This conclusion may be a consideration when pain treatment regimens include analgesia.

References


