The Possible Role of Gonadal Steroids and 5HT$_3$ 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 arachadonic acid, bradykinin and prostaglandin release, initiates vasodilation and extravasation of serotonin which then binds with 5-HT$_3$ 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-HT$_3$ receptors non-competitively, blocking 5-HT$_3$ 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-HT$_3$ receptors in inflammatory pain, discussing the antagonism of 5-HT$_3$ 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-HT$_3$ functionality in human pain and the potential for employing 5-HT$_3$ selective drugs as a method of therapy.

5-HT$_3$ 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-HT$_3$ 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-HT$_3$ is exclusively a ligand gated ion channel [2] and therefore distinct from the predominance of 5-HT$_1$ 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.

Table 1: SHT Family of receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subunits</th>
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<tbody>
<tr>
<td>5-HT$_1$</td>
<td>A B C D E F</td>
</tr>
<tr>
<td>5-HT$_2$</td>
<td>A B C</td>
</tr>
<tr>
<td>5-HT$_4$</td>
<td>A B</td>
</tr>
<tr>
<td>5-HT$_5$</td>
<td>A</td>
</tr>
</tbody>
</table>

Receptor Subunits: A B C D E F

Location and action of 5-HT$_3$ receptors

The 5-HT$_3$ receptor family consists of a ligand-gated ion channel serotonergic receptor existing in two subtypes, A and B (Table 1). The subtype 5-HT$_3$A is distributed both centrally and peripherally while the subtype 5-HT$_3$B is exclusively peripherally distributed [4]. 5-HT$_3$B however, functions only in conjunction with the 5-HT$_3$A subtype and therefore is not a homomeric receptor [5]. Serotonin 5-HT$_3$ receptors have been localized peripherally, in vagus nerve afferents, in the inferior ganglia of the vagus nerve (nodose), in pre- and post-ganglionic autonomic fibers, and in dorsal root ganglia nociceptive afferents [6,7]. Centrally they are found in Rexed’s lamina II (nucleus Substantia Gelatinosa) of the spinal gray dorsal horn and in several supraspinal loci including the area postrema, nuclei of the solitary tract, the nuclei ambiguous, the nuclei accumbens, amygdala, and habenula, the hippocampus and diffusely throughout the cortex [8,9].

Action of peripheral 5-HT$_3$ receptors

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-HT$_3$ 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-HT$_3$ 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 central 5-HT$_3$ receptors

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

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Received November 05, 2011; Accepted January 30, 2012; Published February 06, 2012

Citation: Schultea TD (2012) The Possible Role of Gonadal Steroids and 5HT$_3$ Receptors in Encouraging Menses. Reproductive Sys Sexual Disord 1:104. doi:10.4172/2161-038X.1000104

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Serotonergic fibers from the raphe nuclei contribute to the dorsolateral funiculi which innervate the superficial dorsal horn of the spinal cord [13]. 5-HT3 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-HT3 receptor antagonists blocked 5-HT3-induced analgesia and produced a moderate hyperalgesic response [15]. The reduction of dorsolateral funiculus pathologies caused the release of serotonin at synaptic connections with both nociceptive afferents and interneurons which terminate in stress-responsive interneurons [17].

Published data supports that 5-HT, released from descending dorsolateral funiculus pathologies binds to spinal gray dorsal horn interneuronal 5-HT3 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-HT3 receptors

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<tr>
<th>Antagonism of 5-HT3 receptors by gonadal steroids</th>
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Gonadal steroids probably combine allosterically with 5-HT3 receptors at the receptor-membrane surface [19] (Table 2). The competition between serotonin and gonadal steroids to react with 5-HT3 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-HT3 receptors [20-22]. Further, ovarian hormones play a role in regulating 5-HT3 receptor expression in stress-induced bowel dysfunction [23]. Both the 5-HT3 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 dependent in rats [23,28]. 5-HT3 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-HT3 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) affects 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 mensus [30]. With circulating estrogen levels high, making it more available for binding with 5-HT3 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-HT3 receptor competition as it has been shown in mice [31]. Circulating progesterone levels, in response to luteinizing hormone (LH) 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-HT3 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


