Reproductive System and Sexual Disorders: Current Research

Schultea, Reproductive Sys Sexual Disord 2012, 1:1
DOI: 10.4172/2161-038X.1000104

Research Article Open Access

The Possible Role of Gonadal Steroids and $5HT_3$ Receptors in Encouraging Menses

Thomas D Schultea*

Moody Health Science Center Research Institute, 5912 Spencer Hwy, Pasadena, Texas 77505, USA

Abstract

Serotonin (5-HT) and seritonergic receptors are strategic participants in nociception. Traumatic injury to peripheral tissues which results in arachadonic acid, bradykinin and prostaglandin release, initiates vasodilation and extravisation 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 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 pain afferents and nociception while peripheral serotonergic effects are strongly pro-algesic.

Table 1: 5HT Family of receptors

Location and action of 5-HT_3 receptors

The 5-HT_3 receptor family consists of a ligand-gated ion channel seritonergic receptor existing in two subtypes, A and B (Table 1). The subtype 5-HT_3a in distributed both centrally and peripherally while the subtype 5-HT_3b is exclusively peripherally distributed [4]. 5-HT_3b however, functions only in conjunction with the 5-HT_3a 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].

Receptor	Subunits					
5-HT_1	A	B	C	D	E	F
5-HT_2	A	B	C			
5-HT_3	A	B				
5-HT_4						
5-HT_5	A	B				
5-HT_6						
5-HT_7						

Table 1: 5-HT Receptors.

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_3 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.

***Corresponding author:** Thomas D Schultea, Moody Health Science Center Research Institute, 5912 Spencer Hwy, Pasadena, Texas 77505, USA, Tel: 281-998-6090; Fax: 281-998-508; E-mail: tschultea@txchiro.edu

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

Seritonergic fibers from the raphe nuclei contribute to the dorsolateral funiculi which innervate the superficial dorsal horn of the spinal cord [13]. 5-HT$_3$ 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$_3$ receptor antagonists blocked 5-HT-induced analgesia and produced a moderate hyperalgesic response [15]. The reduction of dorsolateral funiculus modulated anti-nociception by administration of 5-HT$_3$ receptor antagonists suggested that 5-HT$_3$ receptors are involved with the expression of feed back, serotonergic pain modulation at the spinal level [16]. Further, Intraspinal administration of the 5-HT$_3$ 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, released from descending dorsolateral funicular pathways binds to spinal gray dorsal horn interneuronal 5-HT$_3$ receptors, depolarizing them [18]. Interneuron depolarization releases GABA and opioids which inhibit primary and/or second-order nocisponsive neurons [17].

Table 2: Location of 5-HT$_3$ receptors

Antagonism of 5-HT$_3$ receptors by gonadal steroids

Gonadal steroids probably combine allosterically with 5-HT$_3$ receptors at the receptor-membrane surface [19] (Table 2). The competition between serotonin and gonadal steroids to react with 5-HT$_3$ 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$_3$ receptors [20-22]. Further, ovarian hormones play a role in regulating 5-HT$_3$ receptor expression in stress-induced bowel disfunction [23]. Both the 5-HT$_3$ 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$_3$ 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 opoidergic interneurons which terminate on ascending secondary pain afferent (spinothalamic) neurons [21]. As previously stated, 5-HT$_3$ receptors are non-competitively antagonized by gonadal steroids [27,29].

Central	Peripheral
Prefrontal cortex	Pre-ganglionic autonomic neurons
Hippocampus	Post-ganglionic autonomic neurons
Primary Dorsal horn afferents	Vagal neurons
Nucleus Accumbens	Dorsal root ganglia neurons
Area Postrema	C-fiber nociceptive afferents
Limbic System	Other nociceptive afferents

Table 2: 5-HT$_3$ receptor locations.

Discussion

During the initial fourteen days of the female menstral 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 mensus [30]. With circulating estrogen levels high, making it more available for binding with 5-HT$_3$ 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$_3$ receptor competition as it has been shown in mice [31]. Circulating progesterone levels, in response to leutenizing 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$_3$ 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

1. Fawcett D (1986) A Textbook of histology. (11th edn) WB Saunders Company, Philadelphia.
2. Maricq AV, Peterson AS, Brake AJ, Myers RM, Julius D (1991) Primary structure and functional expression of the 5HT3 receptor, a serotonin-gated ion channel. Science 254: 432-437.
3. Boess FG, Martin IL (1994) Molecular biology of 5-HT receptors. Neuropharmacology 33: 275-317.
4. Morales M, Wang, SD (2002) Differential composition of 5-Hydroxytryptamine3 receptors synthesized in the rat CNS and peripheral nervous system. J Neurosci 22: 6732-6741.
5. Dubin AE, Huvar R, D'Andrea MR, Pyati J, Zhu JY, et al. (1999) The Pharmacological and functional characteristics of the serotonin 5-HT3A receptor are specifically modified by a 5- HT3B receptor subunit. J Biol Chem 274: 30799-30810.
6. Fozard JR (1984) Neuronal 5-HT receptors in the periphery. Neuropharmacology 23: 1473-1486.
7. Zeitz KP, Guy N, Malmberg AB, Dirajlal S, Martin WJ, et al. (2002) The 5-HT3 subtype of serotonin receptor contributes to nociceptive processing via a novel subset of myelinated and unmyelinated nociceptors. J Neurosci 22: 1010-1019.
8. Kilpatrick GJ, Jones BJ, Tyers MB (1989) Binding of the 5-HT3 ligand, [3H] GR65630, to rat area postrema, vagus nerve and the brains of several species. Eur J Pharmacol 159: 157-164.
9. Kidd EJ, Laporte AM, Langlois X, Fattaccini CM, Doyen C, et al. (1993) 5-HT3 receptors in the rat central nervous system are mainly located on nerve fibres and terminals. Brain Res 612: 289-298.
10. Sufka KJ, Schomburg FM, Giordano J (1992) Receptor mediation of 5-HT-induced inflammation and nociception in rats. Pharmacol Biochem Behav 41:53-56.
11. Smith H, Jones T, Hunt R (1972) Veterinary Pathology, (4th edn), Lea & Ferbiger.
12. Giordano J, Rogers LV (1989) Peripherally administered serotonin 5-HT3 receptor antagonists reduce inflammatory pain in rats.Eur J Pharmacol 170: 83-86.
13. Martin RF, Jordan LM, Willis WD (1978) Differential projections of cat medullary raphe neurons demonstrated by retrograde labeling following spinal cord lesions. J Comp Neurol 182: 77-88.

14. Giordano J, Barr G (1988) Possible role of spinal 5-HT in mru-and kappa-opoid receptor- mediated analgesia in the developing rat. Devel Brain Res 33: 121-27.

15. Glaum SR, Proudfit HK, Anderson EG (1988) Reversal of the antinociceptive effects of intrathecally administered serotonin in the rat by a selective 5-HT3 receptor antagonist. Neurosci Lett 95: 313-317.

16. Kawamura M, Ohara H, Go K, Koga Y, Ienaga K (1998) Neurotropin induces antinociceptive effect by enhancing descending pain inhibitory systems involving 5-HT3 and noradrenergic alpha2 receptors in spinal dorsal horn. Life Sci 62: 2181-2190.

17. Giordano J (1991) Analgesic profile of centrally administered 2-methvlserotonin against acute pain in rats. Eur J Pharmacol 199: 233-236.

18. Bardin L, Lavarenne J, Eschalier A (2000) Serotonin receptor subtypes involved in the spinal antinociceptive effect of 5-Ht in rats. Pain 86: 11-18.

19. Wetzel CH, Hermann B, Behl C, Pestel E, Rammes G, et al. (1998) Functional antagonism of gonadal steroids at the 5-Hydroxytiiptamine tvpe 3 receptor. Mol Endocrinol 12: 1441-51.

20. Oz M, Zhang L. Spivak CE (2002) Direct noncompetitive inhibition of 5-HT(3) receptor- mediated responses % forskolin and steroids. Arch Biochem Biophys 404: 293-301.

21. Wu FS, Lai CP, Liu BC (2000) Non-competitive inhibition of 5-HT3 receptor-mediated currents by progesterone in rat nodose ganglion neurons. Neurosci Lett 278: 37-40.

22. Barann M, Göthert M, Brüss M, Bönisch H (1999) Inhibition by steroids of [14C]-guanidinium flux through the voltage-gated sodium chamnnel and the cation channel of the 5- Ht3 receptor of NIE-115 neuroblastoma cells. Naunyn Schmiedebergs Arch Pharmacol 360: 234-241.

23. Vinogradova EP, Zuhkov DA, Butuev AS (2003) The effects of stages of the estrus cycle on pain thresholds in female white rats. Neurosci Behav Physiol 33: 269-272.

24. Hallin RG (2003) Pain more painful in women. Gender perspective neglected in research on the biological mechanisms of pain. Lakartidningen 100: 3738-3741.

25. Bradshaw H, Miller J, Ling Q, Malsnee K, Ruda MA (2000) Sex differences and phases of the estrous cycle alter the response of spinal cord dynorphin neurons to peripheral inflammation and hyperalgesia. Pain 85: 93-99.

26. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC (2003) Gender differences in pressure pain threshold in healthy humans. Pain 101: 259-266.

27. Teepker M, Peters M, Vedder H, Schepelmann K, Lautenbacher S (2010) Menstrual Variation in Experimental Pain: Correlation with Gonadal Hormones. Neuropsychobiology 61: 131-140.

28. Martinez-Gomez M, Cruz Y, Salas M, Hudson R, Pacheco P (1994) Assessing pain threshold in the rat: changes with estrus and time of day. Phvsiol Behav 55: 651-657.

29. Giordano J, Schultea T (2004) Serotonin 5-HT3 receptor mediation of pain and anti- nociception: Implications for clinical therapeutics. Pain Physician 7: 141-147.

30. Bullock J, Boyle J, Wang M (1991) Physiology (2nd edn), Williams & Wilkins.

31. Multona, S, Pardutzb, A, Mosena, J (2005) Lack of estrogen increases pain in the trigeminal formalin model: a behavioural and immunocytochemical study of transgenic ArKO mice. Pain 114 257-265.

32. Li TJ, Yu BP, Dong WG, Luo HS, Xu L, et al. (2004) Ovarian hormone modulates 5-hydroxytryptamine 3 receptors mRNA expression in rat colon with restraint stress-induced bowel dysfunction. World J Gastroenterol 10: 2723-2726.