August 3, 2023

«sal» «First» «Middle» «Last_Name»
«title»
«company»
«address1» «add_2»
«city», «state» «Zipcode»

Dear «sal» «Last_Name»,

We are pleased to share with you a working draft of our compilation paper on the peptide relaxin.

Prepare to be amazed about one of the best kept secrets of the human body and animal kingdom that changes how many complex conditions are now approached as it shines light on the marvels of creation and its capacity to communicate, adapt, and change.

We offer deep gratitude to the fruitful work of dedicated researchers whose papers we have summarized and we encourage you to share with us your thoughts and how this may impact your areas of study and practice.

We promote the concept that the human body and really all of creation can best be understood from the perspective of procreation- that is to say that is the primary purpose for which the body was created.

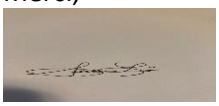
Relaxin is an important conduit in the body and in heredity and we believe it is a reasonable hypothesis to consider whether altered relaxin in parents, through sperm and in the womb, and through breast milk may be a factor in the increased prevalence of sexual/gender dysmorphia as well as other conditions.

It is our hope that this paper will manifest the importance of healthy dialog, understanding and new ways of thinking regarding pharmaceuticals and other factors that can alter relaxin and the promotion of more natural/less radical treatments, such as Gaba and 5-htp in the field of mental health.

We hope to have an electronic copy available of the final paper on our website by the end of the year. If you would like to be emailed an electronic draft or final copy, please email your request.

We thank you for your time and we welcome your thoughts.

Merci,



Susan Lein
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Discoveries Regarding the Peptide Relaxin and their Wide Spreading Applications and Implications

Susan Lein

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Abstract

Until recently little was known about the peptide relaxin other than it was in all mammals and facilitates the spreading of the hips in women when pregnant. It is now known to be involved in several complex conditions including metabolic disorder, rheumatoid arthritis, cancer, cardiac disease, fibrosis, fibromyalgia, autism, schizophrenia, depression, sleep and more. It is known to impact the brain, the heart, vasculature, breasts, lungs, skin, kidneys, liver, gut, bone, uterus, ovaries, testis and prostate.[1] It is also known to be in birds, fish and insects.

To present these exciting findings, nine studies were profiled and direct excerpts were taken and shared. The purpose of this paper is to make the medical community and people in general aware of the magnitude of impact relaxin has in the body and to caution if not prevent the development of pharmaceuticals that alter relaxin without comprehensive knowledge of their potential for impact and to provide insight into perhaps a missing piece of the puzzle when studying complex conditions. Another purpose is to cause marvel at how intricately the body is created and how highly functioning and intelligent it is, it even "talks".

Keywords: relaxin, discoveries, metabolic disorder, cancer, mental health

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Method

The report is a series of direct excerpts from five selected studies and was prepared by a highly trained statistician.

In addition, the researcher personally suffered severe consequences from the pharmaceutical Abilify (aripiprazole) which is now known by her with certainty to alter the peptide relaxin. The personal suffering/physical body damage aided greatly in directing search efforts which was highly beneficial in the early ages of her research.

The five studies selected and profiled in order profiled include:

1. R A D Bathgate 1, M L Halls, E T van der Westhuizen, G E Callander, M Kocan, R J Summers, "Relaxin Family Peptides and Their Receptors" American Physiological Society Physiological Review Volume 93 Issue 1 2013 Jan;93(1):405-80. https://pubmed.ncbi.nlm.nih.gov/23303914/
2. F Dehghan,1 B S Haerian,2 S Muniandy,3 A Yusof,4 J L Dragoo,5 and N Salleh1," The Effect of Relaxin on the Musculoskeletal System" Scandinavian Journal of Medicine & Science in Sports2014 Aug; 24(4): e220–e229. Published online 2013 Nov 28.https://pubmed.ncbi.nlm.nih.gov/24283470/
3. Craig M. Smith,1,2,* Andrew W. Walker,1,2 Ihaia T. Hosken,1,2 Berenice E. Chua,1 Cary Zhang,1,2 Mouna Haidar,1,2 and Andrew L. Gundlach1,2,3,*" Relaxin-3/RXFP3 Networks: An Emerging Target for the Treatment of Depression and other Neuropsychiatric Diseases? Front Pharmacol. 2014; 5: 46. Published online 2014 Mar 21. doi: 10.3389/fphar.2014.00046 https://pmc.ncbi.nlm.nih.gov/articles/PMC3968750/
4. Maivel H Ghattas 1, Eman T Mehanna, Noha M Mesbah, Dina M Abo-Elmatty, "Relaxin-3 is Associated with Metabolic Syndrome and its Component Traits in

Women", Clin Biochem 2013 Jan;46(1-2):45-8. doi: 10.1016/j.clinbiochem.2012.09.018. Epub 2012 Sep 24. https://pubmed.ncbi.nlm.nih.gov/23018057/

5. Semih Erden,1 Kevser Nalbant,2 and İbrahim Kılınç3 "Investigation of Relaxin-3 Serum Levels in terms of Social Interaction, Communication, and Appetite as a Biomarker in Children with Autism" Clin Psychopharmacol Neurosci. 2022 Feb 28; 20(1): 135–142. Published online 2022 Feb 28. doi: 10.9758/cpn.2022.20.1.135 https://pubmed.ncbi.nlm.nih.gov/35078956/

Introduction

Up until the last thirty years, relaxin was thought to be a protein, found in male and female mammals. It is now known to be a peptide in the insulin family. Peptides are short chains of amino acids linked by peptide bonds. Your body makes peptides. Peptides are a strings of amino acids, which are the "building blocks" of proteins but a peptide doesn't have as many amino acids as a protein does.

Up until recently, very little was known about relaxin other than it was in all mammals, male and female and facilitated the spreading of the hips during pregnancy. It is now known that Relaxin is found in insects, birds and fish as well as mammals.

"Relaxin was discovered and named by Dr. Frederick Hisaw following observations of the reproductive endocrinology of the gopher and later the guinea pig. He noticed that there was softening and expansion of the pubic ligament just prior to delivery in the pregnant female that facilitated parturition. In 1926 he showed that the injection of serum from pregnant guinea pigs or rabbits caused relaxation of the pubic ligament of virgin guinea pigs when given shortly after estrus (220). The following year the same relaxing factor was shown to be present in pig corpus

luteum and rabbit placenta (221). The hormone was formally named relaxin after it was extracted from pig corpus luteum in 1930 (165). For the next 15 years or so, relatively little work was done with relaxin, but post World War II there was a reawakening of interest in its physiological role that established properties that would be useful in understanding its roles in pregnancy and parturition."[2 3 4 5]

The relaxin family peptides are a sub-group of the relaxin-insulin peptide family. All peptides within this family have a uniform two-chain structure, with two inter-chain and one intra-chain disulphide bond. In the human relaxin family there are seven relaxin family peptides: the human gene 1 (H1-relaxin), human gene 2 (H2-relaxin, commonly referred to as relaxin and equivalent to other species' relaxin-1) and human gene 3 (H3-relaxin), and the insulin/relaxin-like peptides INSL3, INSL4, INSL5 and INSL6.[6] The relaxin peptides interact with four receptors to perform a variety of physiological functions: RXFP1 and RXFP2 are activated by relaxin and INSL3. RXFP 3 and RXFP4 are activated by relaxin-3 and INSL5, respectively.

"There are seven relaxin family peptides that are all structurally related to insulin. Relaxin has many roles in female and male reproduction, as a neuropeptide in the central nervous system, as a vasodilator and cardiac stimulant in the cardiovascular system, and as an antifibrotic agent. Insulin-like peptide-3 (INSL3) has clearly defined specialist roles in male and female reproduction, relaxin-3 is primarily a neuropeptide involved in stress and metabolic control, and INSL5 is widely distributed particularly in the gastrointestinal tract."[7]

The relaxin-3 receptor, RXFP3, is also a modulator of age related disease, playing a role and having implications for: oxidative stress, DNA damage, epigenetic alterations, nutrient sensing, cell semenence and proteostasis/fibrosis.[8] RXFP3 has implications for age related disorders, including: Alzheimer's disease, anxiety and post-traumatic stress disorder,

schizophrenia, obesity and metabolic dysfunction, ischemic stroke, reproductive aging and even alcohol abuse, for which it may be a future target for treatment.[9] "RXFP3 possesses a strong functional relationship with the aging keystome, GIT2."[10]

Additional studies not included in those profiled for this article have found that relaxin may be an important regulator of inflammation and immune processes and that serum relaxin levels are elevated in multiple sclerosis patients.[11] It has also been hypothesized that a potential role for uterine endometrium through its production of relaxin, a peptide hormone, as a "missing-link" to explain this female predominance, variable clinical course and obstetric complications operating in Systemic Lupus Erythematosus SLE.[12] Relaxin is also hypothesized to play a role in cancer fibrosis and initial results have been promising.[13] Amazingly, it relaxin has been found to "talk", a leading research team investigating the promising anti-fibrotic effects of a drug version of the hormone, relaxin, has discovered that the receptor through which it mediates its therapeutic actions can communicate and/or interact with other receptors in cells that contribute to fibrosis progression. This research may have implications for the design of clinical trials involving relaxin and its concomitant use with other drugs that act on these receptors.[14]

This goal of this conceptual compilation of five studies is to manifest the need for and benefits of a comprehensive perspective of the human body and its balance, alteration, its propensity for self-knowledge and desire for life and inner connectedness. The reality of the immense properties and roles of relaxin promote a need for a culture of sharing and building a body of knowledge and an acknowledgement that oversimplified perspective of "game changing" technologies in medicine can in fact be reckless and dangerous and foreseen to be so suggesting a great moral failure when the best evidence is not widely shared and when real risks and known consequences are ignored while exaggerated benefits are promoted and hoped for by

vulnerable populations at a time of great vulnerability at great financial and human decency cost. Temporal mental health conditions that employ treatments like Abilify that alter the human body in damaging and dangerous ways are not appropriate offerings for potential daily life time treatment and promote a culture of a cascade of pharmaceuticals and ill health as accepted realities of mental health treatment with no accountability or acknowledgement from the manufacturer, ignorance among providers, and no help for the inflicted patients- all under the guise of "blockbuster".

Prepare to be amazed and marvel at the human body as you learn that something thought to have a very limited role in the body is so much more profound in its role and impact and it "talks"!

Findings

Relaxin Family of Peptides and their Receptors:

"Relaxin-3 is the most recently identified relaxin family peptide and was discovered following a search of the human genomic database. Functions likely to be associated with relaxin-3 include stress, memory and appetite regulation."[15] [16] [17] [18] [19]

"RXFP1 is the cognate receptor for human relaxin-2 in humans that is found in a wide range of reproductive tissues including ovary, uterus, placenta, mammary gland, prostate and testis. The receptor is also found in heart, kidney, lung, liver and blood cells as well as in a number of areas of brain such as cortex, organum, vasculosum of the lamina terminals (OVLT) and subfornical organs (SFO). Thus relaxin not only has autocrine and paracrine roles but also acts as a neuropeptide."[20]

"There are seven relaxin family peptides that are all structurally related to insulin."[21]

"Relaxin has many roles in female and male reproduction, as a neuropeptide in the central nervous system, as a vasodilator and cardiac stimulant in the cardiovascular system and as an antifibrotic agent."[22]

"Although the evidence for a role for relaxin-3 in the body is equivocal, there are indications that the peptide may influence food intake."[23]

"There are no studies to date detailing expression of relaxin within human brain. However, in the rat, relaxin mRNA expression in the brain has been detected by RT-PCR (190) and Northern blotting (402). Specific localization of the peptide was also determined by in situ hybridization histochemistry in anterior olfactory nuclei, taenia tecta, and piriform cortex (81, 333, 402), the orbital cortex (333, 402), the fields CA1–2 of Ammon's horn, the dentate gyrus of the hippocampus and the neocortex (402), and the anterior cingulated cortex and the arcuate nucleus(333)."[24] [25] [26] [27] [28] [29]

"Similarly, relaxin-3 expression is highest in the human brain, although substantial expression is also found in the testis, where its role remains to be demonstrated (314). The high levels of relaxin-3 expression in the brain of numerous species have led to a focus on the role of the peptide in the CNS." [30] [31]

"In humans, relatively few studies have been conducted; however, they do suggest similar effects of relaxin on the cardiovascular system. In the clinical trial for scleroderma, long-term (6 mo) infusion of relaxin increased creatinine clearance and produced a modest decrease in blood pressure (149, 527). More recent trials of relaxin for the treatment of cardiac failure have shown that a short (24 h) infusion of relaxin is associated with decreased systemic vascular resistance, serum creatinine, pulmonary wedge pressure, and a small decrease in systolic blood pressure." [32] [33] [34]

"Relaxin also acts directly on the heart. The presence of relaxin receptors (RXFP1) in the heart was first suggested by the demonstration of high-affinity binding sites for relaxin in rat atria (401, 402). Subsequently, in the same species, relaxin was shown to be one of the most powerful inotropic and chronotropic agents known (271). The positive chronotropic effects of relaxin occur in perfused intact hearts (36, 107, 531, 534) and isolated right atria (271, 350, 514, 553, 554), and the positive inotropic effects occur in left atria."[35 36 37 38 39 40 41 42 43 44 45 46 47]

"The effects of relaxin on collagen synthesis and breakdown in reproductive tissues were the first biological effects of relaxin to be recorded (220). Since then it has become evident that relaxin has more general antifibrotic properties (47, 181), and a number of attempts have been made to put these to therapeutic use (462, 526–528, 538). One of the interesting aspects that has emerged is that the antifibrotic properties of relaxin are clearly seen only in disease conditions associated with excessive collagen deposition. Several studies have examined relaxin as a possible treatment for the connective tissue disease scleroderma. Although relaxin was shown to be safe and well-tolerated in clinical trials, and even effective in some patients in a phase II trial (462), it failed to show clinical efficacy in a larger scale phase III trial (149). In spite of these disappointing findings, there has been increasing evidence from animal studies that relaxin has a role in controlling collagen turnover."[48 49 50 51 52 53 54 55 56 57 58]

"There is also now increasing evidence that relaxin is produced by cancer cells and can act in an autocrine manner on RXFP1 receptors expressed on these cells. To date, relaxin has been shown to be expressed by endometrial (273), mammary (522), thyroid (226), and prostate tumors (157, 532). There has long been an association of relaxin with breast cancer (reviewed in Refs. 26, 479), and relaxin treatment of breast cancer cells increases their invasive potential (59). Furthermore, elevated serum relaxin levels have been reported in breast cancer patients and in

patients with metastases (60). It is possible that the relaxin produced by breast cancer cells is involved in tissue remodeling during breast cancer progression (60). Relaxin has also been associated with prostate cancer progression, and blocking the actions of relaxin or RXFP1 in rodent models of prostate cancer results in decreased cancer growth."[59 60 61 62 63 64 65 66 67 68]

"Relaxin-3 and RXFP3 are present in hypothalamic and extrahypothalamic regions involved in the hypothalamic-pituitary-adrenal axis (312, 329, 487, 508). Corticotropin releasing factor (CRF) is synthesized and released from the paraventricular nucleus of the hypothalamus (PVN) in response to stress. Interestingly, RXFP3 is abundantly expressed in the PVN, in addition to other regions commonly associated with stress and anxiety, including the bed nucleus of the s"tria terminalis, lateral septum, periaqueductal gray, and the dorsal raphe."[69 70 71 72 73]

"Although relaxin-3 influences food intake, there is little evidence to suggest that infusion of the peptide increases body weight."[74]

"Much of the evidence for a role for relaxin-3 in behavioral activation and arousal comes from the parallel study of the neuroanatomy of relaxin-3 projections and sites of RXFP3 expression. Structures in the septohippocampal pathway of rodents are heavily innervated by relaxin-3-positive projections from the NI (FIGURE 6). One of the major functions of this pathway is the generation of hippocampal theta rhythm, which has oscillations at 4–12 Hz. Theta rhythm is controlled by pacemaker neurons of the medial septum (MS) and is involved in behaviors such as vigilance, exploration, orientation, navigation, locomotor control, and working memory. The NI has an important role in theta rhythm, and electrical stimulation of the nucleus causes theta rhythm in the hippocampus."[75]

"Serotonin (5-hydroxytryptamine, 5-HT) has well-established roles in cognitive, emotional, and behavioral control (reviewed in Ref. 106). Since the NI is located close to the

dorsal raphé, a region enriched in 5-HT neurons, studies have been carried out examining the effects of 5-HT on relaxin-3 expression (367) and showed that most relaxin-3-containing neurons of the NI coexpress 5-HT1A receptors. Inhibition of 5-HT synthesis for 3 days increased relaxin-3 mRNA in the NI. More studies are needed to determine the relationship between changes in 5-HT levels and relaxin-3 expression."[76] [77] [78]

"Thus the relaxin-3-RXFP3 system has a role in feeding, metabolism, stress, arousal, learning, and memory."[79]

"Since relaxin-3 is produced in GABAergic neurons of the nucleus incertus, it likely acts in concert with GABA signaling. In this way, it may be possible to fine-tune the GABAergic system by targeting RXFP3."[80]

"Relaxin is now emerging as a potential novel treatment for acute congestive heart failure (526). The well-established effects associated with relaxin during pregnancy including increased cardiac output, blood vessel compliance, and renal blood flow (265), together with studies that show positive inotropic and chronotropic effects on the heart (127, 271) and the observation that relaxin plasma levels increase in heart failure (132), suggested that it may have beneficial effects." [81] [82] [83] [84] [85] [86]

"One of the physiological effects of relaxin with broad therapeutic potential is its effects on connective tissue regulation and fibrosis. From a therapeutic viewpoint, relaxin decreases excess collagen deposition in fibrotic lesions, with a conservation of endogenous connective tissue structure (181, 542). Relaxin also exerts anti-inflammatory effects, can inhibit the activation of human neutrophils by pro-inflammatory agents (345), and prevents histamine and granule release by activated basophils (29) and mast cells."[87] [88] [89] [90] [91]

"As discussed in the previous section, relaxin appears to be recruited in many types of cancer cells as an endogenous factor for tissue remodeling. In particular, relaxin is associated with prostate cancer progression, and increased expression of relaxin (but not RXFP1) occurs in prostate carcinomas and prostate cancer cell lines (157, 532, 549). Importantly, downregulation of either relaxin or RXFP1 caused significant inhibition of growth (549) and invasiveness, in addition to increased apoptosis (157) in rodent prostate cancer models. Furthermore, relaxin is associated with increased invasiveness of endometrial (273), breast (59, 60), and thyroid (226) carcinomas, suggesting that agents blocking relaxin action may be used for the possible treatment of multiple cancers."[92 93 94 95 96 97 98 99]

The Effect of Relaxin on the Musculoskeletal System

"Relaxin is a hormone structurally related to insulin and insulin-like growth factor, which exerts its regulatory effect on the musculoskeletal and other systems through binding to its receptor in various tissues, mediated by different signaling pathways."[100]

"Several studies have highlighted the therapeutic potential of relaxin for ectopic pregnancy, male infertility, and heart failure, cardiovascular and musculoskeletal diseases."[101]

"Relaxin1 and 2 reconcile the hemodynamic changes occurring during pregnancy such as cardiac output, renal blood flow, and arterial compliance (Conrad, 2011), as well as weakening the pelvic ligaments for parturition in species such as guinea pigs and mice (Sherwood et al., 1993). RLN3 is a highly conserved neuropeptide in vertebrates, and is involved in a wide range of neuroactivities such as response to stress and cognition, as well as in neurological disease (Smith et al., 2011)."[102 103 104 105]

"Relaxin alters the propensities of cartilage and tendon by activating collengenase. This hormone is also involved in bone remodeling and healing of injured ligaments and skeletal muscle."[106 107 108 109 110]

"Evidence also suggests that the functional domains of RXFP1, the cell type in which it is expressed, and the ligand used to activate the receptor all have important roles in the musculoskeletal system (Fig. 2). Relaxin alters cartilage and tendon stiffness by activating collagenase (Hashem et al., 2006; Pearson et al., 2011). Relaxin is also involved in bone remodeling process and in healing of injured ligaments and skeletal muscles (Li et al., 2005; Dragoo et al., 2009). The soft tissue healing cascade is composed of three phases, inflammation, regeneration, and fibrosis, and relaxin is a regulator of both inflammation and fibrosis (Mu et al., 2010). Relaxin also acts as antifibrotic agent, and favors muscle regeneration and The musculoskeletal system is composed of bone, synovium, ligament, muscle, tendon, articular cartilage, and the related connective tissues that support the body's ability to move (Farley et al., 2012). [111 112 113 114 115 116 117]

"Relaxin in combination with estrogens may also have therapeutic value in the treatment of rheumatoid arthritis (RA) (Santora et al., 2005; Ho et al., 2011)."[118 119 120]

"Relaxin along with hormones such as estrogen and growth factors such as transforming growth factor-beta (TGF-β) helps orchestrate the bone remodeling process."[121]

"A competition exists between fibrosis and regeneration during healing of damage tissue. Relaxin and transforming growth factor-beta1 (TGF-β1) make imbalance between regeneration and fibrosis process. Increased relaxin and decreased TGF- β1 result in regeneration and consequently healing, while decreased relaxin and increased TGF- β1 lead to fibrosis."[122]

Relaxin in combination with estrogens may also have therapeutic value in the treatment of rheumatoid arthritis (RA) (Santora et al., 2005; Ho et al., 2011). Relaxin exerts its anti-inflammatory effect through down-regulation of neutrophil function (Bani et al., 1998) and stimulates leukocyte adhesion and migration in human mononuclear cells (Figueiredo et al., 2006)."[123] [124] [125] [126]

"Relaxin also acts as antifibrotic agent, and favors muscleregeneration and against muscle fibrosis to promote regrowth of myofibers in skeletal muscle healing."[127]

"Fibrosis is the last phase of healing where non-functional scar tissue is formed caused by excessive accumulation of connective tissue following damage."[128]

"Relaxin has been shown to inhibit fibrosis formation"[129]

"Relaxin has been reported to effect tendon metabolism by controlling the length of tendon growth (Maclennan et al., 1986; Wood et al., 2003) and reduce tendon stiffness by increasing tendon laxity through activation of collagenase (Pearson et al., 2011)."[130] [131] [132]"A study in women with normal menstrual cycles who did not take any contraceptive pills demonstrated a significant link between scrum relaxin levels and patellar tendon stiffness." [133]

"A prospective study of elite female athletes illustrated that players with increased serum relaxin levels had an increased risk of an ACL tear compared with females with lower relaxin levels (Dragoo et al., 2011a). Players having a relaxin concentration of greater than 6.0 pg/mL had more than four times greater risk of ACL injury. Other studies have collaborated these findings (Schauberger et al., 1996; Wojtys et al., 2002; Beynnon et al., 2006; Dragoo et al., 2011a)."[134] [135] [136] [137] [138]

Relaxin-3/RXFP3 Networks, An Emerging Target for the Treatment of Depression and Other Neuropsychiatric Diseases?

"Animal and clinical studies of gene-environment interactions have helped elucidate the mechanisms involved in the pathophysiology of several mental illnesses including anxiety, depression, and schizophrenia; and have led to the discovery of improved treatments. The study of neuropeptides and their receptors is a parallel frontier of neuropsychopharmacology research and has revealed the involvement of several peptide systems in mental illnesses and identified novel targets for their treatment. Relaxin-3 is a newly discovered neuropeptide that binds, and activates the G-protein coupled receptor, RXFP3."[139]

"Existing anatomical and function evidence suggests relaxin-3 is an arousal transmitter which is highly responsive to environmental stimuli, particularly neurogenic stressors including hippocampal theta rhythm and associated learning and memory."[140]

"In this regard, it is clear that neuromodulatory systems that utilize monoamine and peptide transmitters play a key role in the neurophysiology of circuits associated with affective behavior and cognition (Hoyer and Bartfai, 2012; Marder, 2012; van den Pol, 2012), and they can be both aberrant in psychiatric pathology and targets for novel treatments (e.g., Domschke et al., 2011; Hoyer and Bartfai, 2012; Lin and Sibille, 2013)."[141] [142] [143] [144] [145] [146]

"Relaxin-3 is a highly conserved neuropeptide that is abundantly expressed in four small groups of largely γ-aminobutyric acid (GABA) projection neurons in mammalian brain (Bathgate et al., 2002; Burazin et al., 2002; Tanaka et al., 2005), and is involved in regulating aspects of physiological and behavioral stress responses and the integration of sensory inputs (see Smith et al., 2011). Recent reviews have highlighted the putative role of relaxin-3 in the control of feeding and the neuroendocrine axis (Tanaka, 2010; Ganella et al., 2012, 2013b). However, existing neuroanatomical and functional evidence also suggests the GABA/relaxin-3 system acts as a broad "arousal" network which is highly responsive to environmental stimuli

(neurogenic stressors) and modulates stress responses and other key behaviors/neural processes. These effects are mediated via a variety of mechanisms, such as influencing hippocampal theta rhythm and associated learning and memory, and via putative actions throughout the limbic system (Tanaka et al., 2005; Ma et al., 2009a, 2013; Banerjee et al., 2010)."[147] [148] [149] [150] [151] [152] [153] [154] [155] [156] [157]

"Since the early discovery of "substance P" (von Euler and Gaddum, 1931), a plethora of neuropeptide-receptor systems have been identified and characterized (see Hoyer and Bartfai, 2012). Neuropeptides are commonly co-released with GABA/glutamate and monoamine transmitters, and generally signal through G-protein coupled receptors to modulate a broad range of neural processes and behaviors. The potential attractiveness of neuropeptide-receptor systems as therapeutic drug targets is enhanced by their high level of signaling specificity. For example, expression of neuropeptides is often restricted to small populations of neurons within a small number of brain nuclei (e.g., orexin, MCH, and neuropeptide S; Xu et al., 2004; Sakurai, 2007; Saito and Nagasaki, 2008), and neuropeptides frequently bind to their receptors with high affinity and specificity due to their generally large allosteric binding sites (Hoyer and Bartfai, 2012). Neuropeptides are also often preferentially released under states of high neuronal firing frequency in response to the nervous system being challenged, as can occur during acute or chronic environmental stress and/or in association with neuropsychiatric disorders (Hökfelt et al., 2000, 2003; Holmes et al., 2003)."[158] [159] [160] [161] [162] [163] [164] [165] [166] [167]

"These characteristics suggest that therapeutic drugs which target neuropeptide systems may be less prone to unwanted "non-specific" side-effects compared to current drug treatments. For example, although tricyclic antidepressants are relatively effective at increasing 5-hydroxytrypamine (5-HT) and noradrenaline signaling to reduce the symptoms of major

depression, they are hampered by cross-reactivity with other transmitter systems and reduce histamine and cholinergic signaling, which contributes to unwanted side effects (Westenberg, 1999). Even their "replacement" drugs (selective serotonin reuptake inhibitors, SSRIs) are associated with shortcomings such as slow onset of action and patient resistance, and side effects including sexual dysfunction, and weight gain (Nestler, 1998). Similar problems have been encountered in the development of antipsychotics to treat schizophrenia (Tandon, 2011), suggesting that more selective drugs that target relevant peptide receptors could have broad therapeutic applications (Hökfelt et al., 2003; Holmes et al., 2003; Hoyer and Bartfai, 2012)."[168] [169] [170] [171] [172] [173] [174]

Relaxin promotes wakefulness. "Considerable neuroanatomical evidence suggests relaxin-3 should be thought of as an arousal neurotransmitter."[175]

Relaxin-3 is Associated with Metabolic Syndrome and its Component Traits in Women

"The metabolic syndrome is a complex of interrelated risk factors for cardiovascular disease (CVD) and diabetes. These factors include dysglycemia, raised blood pressure, elevated triglyceride levels (TG), decreased high density lipoprotein cholesterol level (HDL-C), and obesity (particularly central adiposity). The associations and clustering of these factors have been known for decades."[176]

"There is widespread agreement that atherosclerotic cardiovascular disease (ASCVD) is the major clinical outcome of the metabolic syndrome; all the metabolic risk factors seemingly predispose to the development of ASCVD. The metabolic syndrome is also strongly associated with the development of type 2 diabetes [9,10]."[177] [178] [179]

"In the current study, we sought to evaluate the relation of relaxin-3 to metabolic syndrome and its component traits in women. Our results demonstrated that the risk of metabolic

syndrome increased with rising relaxin-3 levels. This result raises the possibility that relaxin-3 can be a useful marker for metabolic syndrome." [180]

Investigation of Relaxin-3 Serum Levels in terms of Social Interaction, Communication, and Appetite as a Biomarker in Children with Autism

"Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by a restricted and repetitive pattern of behaviors, interests, or activities, as well as limitations in mutual communication and social interaction [1]. ASD prevalence has been reported to have increased, especially in the last 30 years, affecting approximately 2% of children [2]. Despite the increasing number of studies that investigate this disorder, which negatively affects a significant part of society, its etiology remains unclear, and there is no definitive treatment for ASD yet. In addition, one of the important limitations that we face when diagnosing ASD is the fact that the diagnostic process is based on observations and the history provided by the caregiver. Therefore, objective measurements (blood test or radiologic screening) are of importance for elucidating the etiology of ASD, as well as its diagnosis, and/or follow-up. Yet, numerous studies report that there are biologic abnormalities associated with ASD [3]. Biomarkers to be developed to accurately measure these abnormal biological processes may be of importance in the diagnosis, follow-up, and treatment of ASD."[181] [182] [183] [184]

"Restrictions in social behavior are the main symptoms of ASD. The roles of the hippocampus and amygdala in ASD are often investigated because they are involved in the basic functions of the social brain." [185]

"Considering the animal studies investigating the effect of the relaxin-3/RXFP3 system on social behavior, one study found that chronic activation of RXFP3 in the ventral hippocampus

increased social avoidance [14]. In another study, it was stated that central relaxin-3/RXFP3 activation disrupted social recognition, and that as a result of this activation there was a functional interaction between RXFP3 and oxytocin receptors in the amygdala, where this interaction might be effective in modulating social memory [15]. These results, showing the link between relaxin-3 and oxytocin, suggest that relaxin-3 may also play a role in ASD."[186] [187] [188]

"RXFP3 is also found in hypothalamic regions closely related to appetite control and hormonal balance [16]. Acute RXFP3 activation has been shown to consistently increase food intake in satiated adult male rats [17]. Sub-chronic intracerebroventricular (ICV) administration of relaxin-3 resulted in a significant increase in average daily food intake and a cumulative increase in body weight [18]. Oxytocin and arginine vasopressin are the hormones that strongly affect nutritional behavior. In both animals and humans, oxytocin has been shown to act as an anorexigenic signal [19,20] and deficiencies in oxytocin synthesis have been shown to lead to hyperphagia and obesity [21]."[189] [190] [191] [192] [193] [194] [195]

"In this study, serum levels of relaxin-3 were compared between children with ASD and control group of similar age, sex, and socioeconomic level. In support of the hypothesis, our findings found that serum relaxin-3 levels were higher in children with ASD than in the controls. No statistically significant correlation was found between relaxin-3 levels and CARS total scores in the group with ASD, but the listening response sub-scale score of CARS was found to negatively correlate with the level of relaxin-3. Furthermore, as relaxin-3 levels increased in children with ASD, it was found that the speech problem sub-scale score on the ABC scale and the desire to drink score on the CEBQ scale increased, but the satiety responsiveness and food fussiness scores decreased. These results showed that levels of relaxin-3 were associated with

listening, speech difficulties, and appetite problems in children with ASD as reported by their parents."[196]

"Relaxin-3 serum levels, which are believed to function in stress, excitation, and memory, were investigated in our study [6]. According to these results, relaxin-3 may have an effect on speaking from verbal communication skills and listening from non-verbal communication skills." [197]

Conclusions

Relaxin presents a profound discovery about the human body that has ramifications for understanding complex condition and developing safe and effective therapies. The discoveries regarding relaxin are perhaps the most profound discoveries regarding the human body in the last fifty years, if not century. As relaxin has an enormous impact and potential for impact on the human body, a thorough yet streamlined base of knowledge is necessary for practioners, researchers, and drug developers and drug evaluators and even patients.

Given that it is now known that relaxin plays a role in a wide variety of complex conditions for which there is a great deal of lack of understanding it is important that the encompassing role relaxin plays in the human body be thoroughly taken into condition when developing therapies that alter relaxin, especially for mental health where the treatments are frequently, daily and cumulative. Many psychiatric drugs are known to cause metabolic disorder, sexual dysfunction and change in appetite and weight gain and it is logical to hypothesize that relaxin may be in play for these effects. A greater understanding of relaxin, if taken into consideration when developing new therapies and re-evaluating existing therapies has the propensity to provide safer treatments and the supplement Gamma aminobutyric acid

(GABA) and 5-hydroxytryptamine (5-HT) that are known to be impacted by relaxin warrant consideration for mental health.

Footnotes

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No potential conflict of interest relevant to this article was reported.

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