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Research Article

5-Ht Receptors, Signaling Pathways and Effects, Mechanisms of Action of The Tachykinin System and Its Receptors

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Abstract

We conducted a comprehensive search of the literature to identify all original studies and review articles on 5-HT receptors, signaling pathways and effects on the immune system, mechanisms of action of the tachykinin system and its receptors, and to assess their potential role in the pathogenesis of various diseases.

Keywords: 5-HT; LP-211; LP-44; LP-21; AS-19; SB 269970; 5-HT physiology; 5-HT receptor mechanism of action; 5-HT receptor signaling pathway; 5-HT receptor effect; 5-HT receptor distribution; inflammation; dendritic cells; microglia; macrophages and lymphocytes; tachykinins; neurokinin; substance P; G protein-coupled receptor (GPCR); mutagenesis; peptide interaction; cross-reactivity

Introduction

Serotonin is a well-known neurotransmitter that is synthesized from the amino acid tryptophan. Over the last several years the use of molecular cloning technology has revealed a vast diversity among serotonin (5-HT) receptors, where by what was previously thought to be a family of three pharmacologically defined classes of 5-HT receptors is actually composed of seven distinct subfamilies designated 5-HT1–7. The 5-HT1, 5-HT2, and 5-HT5 subfamilies currently consist of five, three and two subtypes respectively while the 5-HT3,5-HT4, 5-HT6, and 5-HT7 "subfamilies" have at present one subtype each. Fourteen separate genes encode 13 receptors which fall in the superfamily of G protein-coupled receptors and one ligand-gated ion channel receptor [1]. In recent years, our view of serotonin has become tremendously complex as we have learned that multiple specific proteins mediate each of the steps of receptor binding, re-uptake and degradation. The advent of molecular techniques has provided a structural basis for sub-classifying and expanding the large family of serotonin receptors; at present, at least 15 mammalian serotonin receptors have been identified. A wide functional diversity exists within this family: serotonin receptors may be ionotropic or metabotropic, and may couple via G proteins to numerous intracellular signaling pathways. Serotonin receptors also display specific patterns of expression both during development and in the mature animal. The pathways involved in serotonin re-uptake and degradation add further layers of complexity to serotonin biology [2]. Despite their distinct characteristics and functions, these receptors' subtypes share common structural features and signaling mechanisms. Understanding the structure, functions and pharmacology of the serotonin receptor family is essential for unraveling the complexities of serotonin signaling and developing targeted therapeutics for neuropsychiatric disorders [3]. Serotonin signaling is involved in many aspects of behavior and cognition, and dysfunction of the serotonergic system is implicated in psychiatric disease. It is the most common target of psychiatric drugs, and many psychotropic chemicals like psilocybin and LSD act on serotonin receptors. Efforts to understand how serotonin influences behavior have been hindered by its complexity. The neurons that release serotonin are functionally diverse, project broadly throughout the brain, and exert their effects via 14 different receptors. Developing an integrative framework for serotonergic function that relates anatomy, receptors, circuits, and behavior across a whole nervous system would greatly aid our understanding of this important neuromodulatory system [4]. Understanding the neurobiological underpinnings of depressive disorder constitutes a pressing challenge in the fields of psychiatry and neurobiology. Depression represents one of the most prevalent forms of mental and behavioral disorders globally. According to the World Health Organization, an estimated 3.8% of the global population grapples with

depressive disorder, encompassing 5% of adults and 5.7% of adults aged 60 years or older. Notably, women are disproportionately affected by depressive disorders. Depression ranks as a leading cause of disability on a worldwide scale. Studies have illuminated that 15% of patients undergoing treatment for depression ultimately succumb to suicide, contributing significantly to a reduced life expectancy and elevated mortality risk associated with depression [5].

Clinically, depression manifests as an exceedingly heterogeneous disorder, influenced by an array of factors, spanning social, genetic, biological, and psychological dimensions. Clinically, depression manifests as an exceedingly heterogeneous disorder, influenced by an array of factors, spanning social, genetic, biological, and psychological dimensions. The pathogenetic mechanisms underpinning depressive disorder, as well as the overarching comprehension of neurochemical systems linked to mood disorders, remain intricate and only partially elucidated. Depression is posited to stem from the dysfunction of multiple neurotransmitter systems, notably including the serotonergic system. Serotonin (5-HT), a pivotal neurotransmitter, assumes a role in regulating sleep, learning, mood, and appetite. The efficacy of contemporary antidepressants is closely intertwined with their capacity to augment serotonin neurotransmission in some manner. Indeed, serotonin receptors, serving as the targets for serotonin, are also implicated in the pathogenesis of depressive disorders. Moreover, serotonin, beyond its classical role as a neurotransmitter, plays a significant part in the regulation of neuronal development, encompassing processes like neurite outgrowth, somatic morphology regulation, axonal growth cone motility, and dendritic spine shape modulation [5].

The tachykinins, exemplified by substance P, are one of the most intensively studied neuropeptide families. They comprise a series of structurally related peptides that derive from alternate processing of three Tac genes and are expressed throughout the nervous and immune systems. Tachykinins interact with three neurokinin G protein-coupled receptors [10]. NK1R and NK2R are expressed in the central and peripheral nervous system, in the gastrointestinal system, and in immune cells [15]. NK3R receptors are found primarily in the central nervous system. The functions of tachykinins have mainly been determined by their location and distribution [11]. The receptors belong to the G protein-coupled receptor (GPCR) superfamily and consist of three members: NK1R, NK2R, and NK3R, each with its own natural high-affinity peptide ligand (NK1R: substance P [SP], NK2R: neurokinin A [NKA] and NK3R: neurokinin B [NKB]. The three endogenous ligands are highly homologous and share a conserved C-terminal sequence motif known to stimulate some activity towards either of the three NKRs [12]. Tachykinin signaling is involved in a broad range of human physiology, and represents a therapeutic target for multiple pathologies ranging from inflammation and pain to cancer [15]. Tachykinins participate in important physiological processes in the nervous, immune, gastrointestinal, respiratory, urogenital, and dermal systems, including inflammation, nociception, smooth muscle contractility, epithelial secretion, and proliferation. They contribute to multiple diseases processes, including acute and chronic inflammation and pain, fibrosis, affective and addictive disorders, functional disorders of the intestine and urinary bladder, infection, and cancer [10]. Although the NKRs are attractive drug targets widely spread in cells of diverse tissues, only the effective treatment of chemotherapy-induced nausea and vomiting (CINV) has materialized by NK1R antagonists. Still, the intense historical interest in NKR antagonists has indeed resulted in a wealth of highly potent non-peptide compounds for possible drug development [12]. Genetic association studies have implicated a role of neurokinin receptors in alcohol abuse, attention deficit hyperactivity disorder, and bipolar disorder [19]. Neurokinin receptor antagonists are selective, potent, and show efficacy in models of disease. In clinical trials there is a singular success: NK1R receptor antagonists to treat nausea and vomiting [10]. Due to these diverse physiological roles, antagonists of the tachykinin receptors have been tested in clinical trials for neuropathic pain, major depressive disorder, chemotherapy-induced nausea and vomiting (CINV), irritable bowel syndrome (IBS), and schizophrenia [15]. Several selective NK2R antagonists have been considered for the treatment of anxiety disorders or asthma; their receptor interaction mode has been discussed based on sequence comparisons [12]. Despite good safety and tolerability, the preclinical promise of tachykinin receptor antagonists based on animal studies has not been matched by success in the clinic, especially for neuropsychiatric disorders. One contributing factor may be the complex overlap between expression patterns and functions of the receptors and neuropeptides. In CINV, where substance P plays a dominant role, selective NK1R blockade is sufficient. In other cases, such as IBS or depression, targeting multiple subtypes may be required for efficacy[15]. However, there are many plausible explanations for these failures, including an inadequate understanding of disease mechanisms, the poor predictive value of animal models, and the inherent redundancy of the tachykinin system [10]. As a member of the neurotransmitter tachykinin family, substance P (SP) can effectively combat the elevation of blood pressure caused by norepinephrine and angiotensin II and also can lower blood pressure, relax blood vessels, and increase blood flow volume in a short time. SP can inhibit the collagen synthesis of cardiac fibroblasts and plays a potential protective role in the process of myocardial remodeling and myocardial fibrosis, which are of great significance in the clinical treatment of retroperitoneal fibrosis of myocardial infarction [13]. Through activation of NK1R, substance P modulates a wide variety of physiological and disease processes including nociception, inflammation, and depression [15]. Since the discovery that the highest concentration of SP occurred in the substantia nigra, the effects of SP on dopaminergic neurons have been widely studied. It has been shown that SP and NKA both cause release of dopamine in the striatum, although there has been some controversy over the most potent tachykinin in this pathway. Disruption of this pathway produces the parkinsonian features of rigidity and bradykinesia [11]. Mounting evidence suggests that neurokinin B (NKB) plays an essential role in sexual maturation and fertility by directly stimulating the release of kisspeptin, with the contribution of additional tachykinins (NKA and SP) in the fine tuning of the activity of Kiss1 neurons. The expression of tachykinins increases in the hypothalamus before puberty and, therefore, they are considered as initiators of pubertal development by stimulating the awakening of Kiss1 neurons [14]. New information about the involvement of tachykinins in infection, fibrosis, and pruritus justifies further trials. A deeper understanding of disease mechanisms is required for the development of more predictive experimental models, and for the design and interpretation of clinical trials [10].

Results and discussion:

Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine that exerts diverse functions in both the central nervous system and peripheral organs. 5-HT is known as a neurotransmitter in the brain that modulates mood, sleep, behavior, appetite and so on. For synthesis of 5-HT, the amino acid, tryptophan, is converted to 5-hydroxtryptophan (5-HTP) by the rate-limiting enzyme, tryptophan hydroxylase (TPH), and then to 5-

HT by aromatic acid decarboxylase. In the early 2000s, two isoforms of TPH were identified and found to be expressed in a mutually exclusive pattern: TPH1 is expressed in peripheral non-neuronal tissues, and TPH2 is expressed in the central nervous system and peripheral neuronal tissues [6]. The general architecture of 5-HT receptors follows the canonical class A GPCR structure characterized by an amino terminus located externally, seven TM helices with hydrophobic regions, three extracellular and three intracellular domains, and a carboxy terminus positioned intracellularly. Residues within the TM domains bind to the receptors, whereas the intracellular domains interact with various cytoplasmic proteins to initiate the downstream signaling pathways. Despite the TM domains being fairly comparable, with minor variations in tilt and twist, there is significant diversity observed in the loops, particularly in extracellular loop 2 (ECL2). The conserved residues are identified using the Ballesteros-Weinstein numbering system which serves as an indicator of the correct residue position in the transmembrane of the GPCR family. The 3D structures of all 12 serotonin receptors have been determined using X-ray crystallography and cryo-electron microscopy (cryo-EM) [3]. The classification of 5-HT receptors can also be based on their coupling with specific G proteins. For instance, the 5-HT1 and 5-HT5 subtypes couple with Gi/o protein, leading to the inhibition of adenylyl cyclase (AC) activity and a reduction in cyclic adenosine monophosphate (cAMP) levels. On the other hand, 5-HT2 couples with Gq/11 protein, stimulating phospholipase C, which leads to elevated levels of inositol triphosphate and calcium ions (Ca2+). The 5-HT4, 5-HT6 and 5-HT7 receptors couple with the Gs protein to enhance AC activity and elevate cAMP levels. Notably, 5-HT4 can bind to both Gs and Gi proteins with preference for Gs over Gi. Each subtype has unique characteristics and functions, although they share common structural features and signaling mechanisms. Apart from the typical coupling with G proteins, GPCRs have been discovered to participate in alternative signaling pathways through the recruitment of arrestins which results in GPCR desensitization. GPCR desensitization involves GPCR kinases (GRKs) being recruited to the receptor, subsequently phosphorylating it, and then β-arrestin binding, which sterically hinders further G protein coupling and leads to desensitization. Biased signaling is usually observed in 5-HT2, where certain ligands selectively activate specific signaling pathways [3]. 5-HT exerts its biological functions through different mechanisms. To date, seven 5-HT receptor (HTR) families have been identified. Most of the identified HTRs are G-protein-coupled receptors; an exception is HT3, which is a ligand-gated ion channel. 5-HT acts as a pan-agonist to these receptors, whereas certain chemical species, including phospholipids (e.g., phosphatidylinositol 4-phosphate) can modulate the activity of G protein-coupled receptor-type HTs. 5-HT can act intracellularly through serotonylation of cytoplasmic proteins, which directly modulates their functions. 5-HT also binds to histones to modify histone codes and, thereby, epigenetically regulate gene expression. Furthermore, 5-HT is an indole derivative that acts to scavenge oxidative stress molecules in the cellular environment [6]. 5-HT1A receptors are inhibitory G-protein coupled receptors (GPCRs). Early studies identified that 5-HT1A receptors function by coupling to Gi/Go proteins in most cells. Extracellular receptor binding of serotonin or 5-H1A agonists leads to intracellular exchange of GDP for GTP on Gi/Go alpha subunits. This, in turn, inhibits adenylyl cyclase, which reduces cAMP levels and protein kinase A activity [7]. In addition to their canonical function, 5-HT1A receptors activate growth factor-regulated signaling pathways, such as mitogen-activated protein kinases (MAPK) and Akt signaling pathways. In MAPK signaling, ERK is preferentially affected by 5-HT1A receptors. For example, in RN46A cells, a model of serotonergic raphe neurons that express endogenous 5-HT1A receptors, adenylyl cyclase and ERK1/2 phosphorylation were inhibited by 5-HT1A-receptor activation. However, in hippocampal-derived differentiated HN2-5 cells, 5-HT1A agonists increased ERK phosphorylation and activity.

These and other studies suggest that the modulation of ERK may depend on neuronal origin, as well as maturation states [7]. Considerable experimental evidence suggests a connection between depressive disorders and alterations in the expression and function of the 5-HT1A receptor in the brain, although findings from such studies often diverge. For instance, an increase in the number of 5-HT1A autoreceptors has been reported in the postmortem brain of individuals who died by suicide due to depression and in cases of bipolar depression, patients with depression and in in vivo experiments in the paraventricular nucleus and hippocampus in rats[5].

On the contrary, in various studies, the 5-HT1A receptor antagonist WAY-100635 attenuated the antidepressant effects of different drugs. An increase in depressive symptoms in rodents when using the antagonist WAY-100635 has also been observed. Concurrently, the activation of postsynaptic 5-HT1A receptors with F15599, a biased 5-HT1A agonist, or the non-selective agonist F13714 has elicited antidepressant-like effects. This divergence may be attributed to functional distinctions between 5-HT1A autoreceptors and heteroreceptors. While 5-HT1A is expressed both as a presynaptic autoreceptor in serotonergic neurons of the raphe nuclei and as a postsynaptic receptor in various brain regions, including the hippocampus and cerebral cortex, these receptors exhibit distinct responses to stimulation. Specifically, chronic stimulation of 5-HT1A receptors has been demonstrated to lead to functional desensitization, but this effect is observed exclusively in presynaptic 5-HT1A autoreceptors[5].

The 5-HT2 receptor family consists of 5-HT2A, 5-HT2B and 5-HT2C subtypes. Although primarily Gq/11-coupled, 5-HT2A and 5-HT2 also recruit β-arrestin-2 upon lysergic acid diethylamide (LSD) and ergotamine binding. These receptors are widely distributed in the brain and peripheral tissues, with 5-H2AR contributing to vascular tone regulation, mood, cognition and hallucinogenic effects. Selective modulation of 5-HT2A is a potential treatment option for various neuropsychiatric conditions and neurological disorders. 5-HT2B are found in the smooth muscle cells, cardiac tissue and endothelial cells, playing a role in cardiovascular function. 5-HT2C are present in the gastrointestinal tract and are involved in gut motility and appetite regulation. Consequently, they are a pharmacological target for anti-obesity drugs [3].

The functional 5-HT3 receptor, like other Cys loop receptors, is a pentameric assembly of five identical or non-identical subunits that surround, in a pseudo-symmetric manner, a water-filled ion channel. Each subunit has a large extracellular domain (ECD) that forms the ligand-binding site, a transmembrane domain (TMD) consisting of four membrane-spanning α-helices (M1–M4) that enable ions to cross the membrane, and an intracellular domain (ICD) formed by the large M3-M4 intracellular loop, which is responsible for receptor modulation, sorting, and trafficking, and which contains portals (openings) that influence ion conductance [8]. Five distinct 5-HT3 receptor subunits (A–E) have been identified so far, which is relatively few for a Cys loop receptor, although the repertoire is increased by a number of different isoforms. There are, for example, a long and short form of the human 5-

HT3A subunit that differ by 32 amino acids, three translational variants of the human 5-HT3B subunit, and five isoforms of the 5-HT3E subunit. The stoichiometry of heteromeric receptors is still not clear, although it has been established that only 5-HT3A subunits can form functional homomeric 5-HT3 receptors, and the presence of at least one 5-HT3A subunit appears to be obligatory in heteromeric receptors [8].

Homomeric 5-HT3A receptors mediate rapidly activating and desensitizing inward currents, which are carried primarily by Na+ and K+ ions. The receptors are also permeable to Ca2+ and other small organic cations. As in other Cys loop receptors, the residues that line the ion-accessible inner face of the M2-generated pore are predominantly non-polar, and it is M2 residues that primarily control ion flux and size selection through the channel.

5-HT3B receptor subunits do not form functional homomeric receptors but can coexpress with A subunits to yield heteromeric 5-HT3AB receptors that differ from 5-HT3A receptors in their EC50, Hill slope, desensitization kinetics, calcium permeability, shape of current-voltage relationship, and, most noticeably, single-channel conductance, which is much larger: ~16 pS in 5-HT3AB receptors compared with <1 pS in 5-HT3A receptors [8].

The 5-HT5 receptor subfamily consists of two receptors, 5-HT5A and 5-HT5B. The two receptors have a 69% similarity in their amino acid composition and a 23-34% similarity with the remaining 5-HT receptors. 5-HT5B are specific to the brain and are not present in humans. 5-HT5A are mainly located in the brain regions responsible for memory and learning, and they play a role in neurotransmitter release and synaptic plasticity. The human 5-HT5A receptor remains largely mysterious and poorly understood compared to other serotonin receptors [3].

Four structures of 5-HT5A have been determined in the presence of two full agonists, 5-CT and methylergometrine, one partial agonist lisuride and antagonist AS2674723. Compared to the 5-CT and methylergometrine bound 5-HT5A-Gi structure, lisuride forms weaker interactions with TM3 and TM6 resulting in the pan agonism of lisuride. The inactive state structure of 5-HT5A bound to antagonist AS2674723 revealed that the tetrahydroisoquinoline ring, guanidine group, and a trifluorophenyl ring in the AS2674723 interacts with the OBP and EBP by hydrophobic interactions, π–π interactions and salt bridge. Particularly, the formation of a salt bridge by guanidine with $E101^{2.65}$ is accompanied by a shift in the extracellular end of TM2 compared to the active state structures. Two less conserved residues in the 5-HT receptors, the $L324^{7.39}$ and $E101^{2.65}$, play a role in determining the selectivity of AS2674723 for 5-HT5A. 5-HT7 has aspartate in place of glutamate at position 2.65 which can form similar electrostatic interactions with the guanidine group of AS2674723, explaining the off-target effect of this ligand for 5-HT7. The inactive 5-HT5A structure also showed a kinked structure in the intracellular end of TM5, which may inhibit signaling activation through the blockage of TM6 movement. This type of interface is present only in 5-HT1E, 5-HT1F, 5-HT5A and 5-HT7 among all serotonin receptors offering potential opportunities for designing inactive state structures of these receptors [3].

The 5-HT7 is a G-protein-coupled receptor (GPCR) with positive coupling to adenylate cyclase stimulating the production of cAMP. Parallel research indicated that its activation, in COS-7 or HEK-293 transfected cell lines, induced increases in adenylate cyclase activity. Using RT-PCR analyses, it has been shown that 5-HT7 mRNA is expressed in the forebrain, brainstem and cerebellum, as well as in the periphery such as the heart and intestine. Northern blot analyses have demonstrated that 5-HT7 mRNA is highly expressed in the hypothalamus, thalamus, hippocampus, and brainstem; however, low densities were also found in the cerebral cortex, striatum, and olfactory tubercle of the guinea pig. Furthermore, ligand binding studies using [3H]-5-carboxamidotryptamine (5-CT) demonstrated that the receptor is localized in cortical layers I–III, septum, thalamus, hypothalamus, hippocampus, amygdala, periaqueductal gray matter, and superior colliculus of the rat [9].

Amino acids and their derivatives play an important role in the functioning of the brain, both in normal and pathological conditions, participating in the biosynthesis of membrane and signal protein and peptide molecules, some lipids, vitamins, hormones and biogenic amines, and are also directly involved in the implementation of neurotransmitter functions, regulation of the activity of excitation and inhibition processes (glutamate, aspartate, GABA. Aromatic amino acids (phenylalanine, tyrosine, tryptophan, histidine) are of particular importance as precursors of catecholamines and serotonin [21]. Changes in the pool of amino acids in rats with ischemic brain injury of varying severity were studied with partial (one-sided ligation of the common carotid artery, CCA), subtotal (simultaneous bilateral ligation of both CCAs), stepwise subtotal (alternate ligation of both CCAs at different time intervals) and total (complete cessation of cerebral blood flow) CI [22]. In partial cerebral ischemia (PCI), the following changes in the pool of amino acids (AA) were noted: an increase in the level of glutamate and GABA without changing the ratio of the content of excitatory and inhibitory amino acid transmitters, an increase in the content of L-arginine, a decrease in the level of essential AAs with an increase in the "Nonessential/Essential" AA ratio, as a reflection of the increased utilization of essential AAs [21]. Changes in sulfur-containing AAs (cysteine, cystathionine, taurine, cysteine sulfonic acid) were absent, except for a decrease in the content of methionine in the parietal lobe, which indicates minor violations of the prooxidant-oxidant balance in this model of CI. There was a decrease in the content of branched hydrocarbon amino acids (BHAAs) and a trend towards a decrease in the level of aromatic AAs (tyrosine, tryptophan, phenylalanine), with a decrease in their ratio, as a reflection of a more pronounced utilization of BHAAs, compared with aromatic AAs [23].

Tachykinins belong to the group of active neuropeptides expressed in the central nervous system and in the peripheral neuronal and non-neuronal tissues. Tachykinins family encompasses: substance P (SP), neurokinin A (NKA), neurokinin B (NKB), neuropeptide-K (NPK), neuropeptidegamma (NP-gamma), hemokinin-1 (HK1) and neurokinin A and neurokinin B (NKA and NKB). Their structure reveals similarity at C-terminus: Phe-X-Gly-Leu-Met-NH2 (X stands for aromatic residue: Tyr or Phe) or branched aliphatic chain (Val or Ile); while it varies at N-terminal. Tachykinins origin from large protein precursors: preprotachykinin A (SP, NPK, NPA, NP-g) and preprotachykinin B (NPB). These precursors are highly homologous. The biological activity of tachykinins is mediated through three different membrane receptors, named tachykinin NK1R, NK2R and NK3R receptors. Tachykinin receptors belong to the class A (rhodopsin-like) of G protein-coupled receptors; they are encoded by TACR1, TACR2 and TACR3 genes, respectively. Tachykinins are characterized by differential binding affinity at NK receptors: SP presents highest affinity at NK1R, NKA is the most potent ligand of NK2R receptor and NKB for NK3R. However, besides high affinity of NKA at NK2R receptors and NKB at NK3R, these tachykinins exhibit also significant affinity at NK1R [18]. A number of

neuropathophysiological processes have been related to the misfunction of tachykinin systems (mostly SP and NKB) in anxiety, learning, fear conditioning or cognitive behavior [14]. The major source of tachykinins in the GI tract are enteroneurones from both, myenteric and submucosal plexuses, and nerve fibers from vagal ganglia and dorsal root. Interestingly, in the stomach they are expressed only in the myenteric plexus. Tachykinins are also present in enterochromaffin and GI-mucosal immune cells. In humans' concentration of SP and NKA in the mucosal and submucosal layers is almost equal or even higher than in the external muscle layers, in contrary to other mammalians (i.e., pigs, rats and rabbits), where their concentration is higher in external muscle layers [18]. Despite sharing a common C-terminal sequence of Phe-X-Gly-Leu-Met-NH2 that helps direct biological function, the peptide ligands exhibit some degree of cross-reactivity toward each other's non-natural receptor. Interestingly, NKA binds to NK1R with fair affinity, whereas SP binds poorly to NK2R. The binding affinity of SP to NK2R is reduced by a factor of 1700 as compared to its binding affinity to NK1R, whereas for NKA, the binding affinity is only reduced by a factor of 37 when it binds to NK1R. The results highlight that while SP effectively activates NK1R, it exhibits only weak activation of NK2R. In contrast, NKA demonstrates the ability to activate both receptors. This finding suggests that NKA exhibits a broader activation profile compared to SP [12].

The tachykinin NK1R receptor is widely distributed in both central and peripheral nervous systems. In the central nervous system, the NK1R is found in high concentration in the dorsal horn of the spinal cord, particularly in layers 1 and 2 where they are located postsynaptic to sensory nerve terminals. There is also a population of NK1R receptor-immunoreactive neurons in layers 3 and 4, whose dendrites arborize with those in layers 1 and 2. In the ventral horn and intermediolateral cell column, NK1R are located on autonomic and motor neurons. High densities of NK1R receptor-binding sites are found in the striatum, stria terminalis, septohippocampal nucleus, and the accumbens nucleus, with moderate densities in the amygdala, habenula, periventricular nucleus, and the olfactory bulb. NK1R are also found on glial cells [11]. Encoded by TAC1R, NK1R is found on chromosome 2 in humans and consists of seven hydrophobic transmembrane domains, three extracellular and three intracellular loops. Two isoforms of NK1R are found in neuronal and immune cells – full-length and truncated NK1R (NK1R-T). The full-length NK1R consists of 407 amino acid residues and one C-terminal intracellular domain, whereas NK1R-T is composed of 311 amino acids and lacks the C-terminal intracellular domain [16]. An established function of NK1R signaling induced by substance P is to serve as a sensory mechanism for noxious stimuli. Thus, NK1R in the medulla controls emesis in response to ingestion of toxins, and substance P released from dorsal root ganglia neurons regulates pain transmission. NK1R and NK2R in peripheral tissues are involved in inflammatory processes, and expression of these G-protein–coupled receptors (GPCRs) is also up-regulated by inflammation [15]. One prominent function of the NK1R is the regulation of stress responses. Following exposure to stressors, SP is released and activates the NK1R in regions such as the lateral septum and the amygdala. Another neurochemical effect of stress exposure is the release of monoamine transmitters into the cortex, and this has been shown to be NK1R-dependent [19].

NK2R receptors are mainly located in peripheral tissues and for some time there was some controversy over whether they were present at all in the central nervous system. Highly selective radioligands now available show highest NK2R receptor densities in the hippocampus, septum, and thalamus with much lower densities elsewhere in the brain. NK2R in the spinal cord are only associated with the dorsal horn, presumably the sensory afferent system [11].

In contrast, expression of NK3R is largely restricted to the nervous system, and signaling induced by NKB regulates neurotransmitter systems as well as secretion of reproductive hormones (GnRH and LH) [15]. NK3R receptors are found primarily in the central nervous system, most notably in the neocortex, septum, diagonal band of Broca, hypothalamus, zona incerta, amygdala, substantia nigra, and raphe nuclei. In contrast to the NK1R receptor, NK3R receptors are dense in the deep layers of the cerebral cortex. Because NK3R-binding sites are found in a similar distribution to central NK2R receptors, there is some suggestion that NK2R receptors are really NK3R receptors [11]. Its endogenous ligand, neurokinin B (NKB), is similarly dispersed in brain with NKB soma present at all levels of the neuraxis. The distribution of NKB terminals and the NK3R overlap with a variety of systems, including those that process reward, fluid balance and vasopressin release, cardiovascular function, locomotion, pain, psychiatric disorders, temperature regulation, and reproduction. Furthermore, dysfunction in the signaling function of the NK3R has profound effects. Mutations in the TACR3 gene encoding NK3R causes hypogonadotropic hypogonadism and infertility. NK3R's are also implicated in the hypertension and blockade of the receptor prevents the systemic release of vasopressin and has a anti-hypertensive action. In addition, NK3R's are a potential therapeutic target to treat gastrointestional pain, anxiety, and psychotic disorders, particularly schizophrenia [17]. Like the NK1R, the NK3R is expressed widely throughout the brain in regions that mediate affective and motivated behaviors, including in the olfactory bulb, amygdala, multiple cortical regions, hypothalamic subnuclei, hippocampus, locus coeruleus, VTA, and interpenduncular nucleus, among others. Overall, NK3R activation has very similar effects to NK1R stimulation on mesolimbic DA function. For example, NK3R stimulation increases the firing rate of dopaminergic neurons of the substantia nigra pars compacta and VTA. In agreement with this, NK3R activation in dopaminergic cells of the midbrain induces transmitter release in the striatum, an effect that is also observed for acetylcholine release in from septal inputs to the hippocampus [19]. In general, both NK1R and NK3R activation has a positive, stimulatory effect on dopaminergic signaling in the mesolimbic pathway. This pathway, which originates in the ventral tegmental area (VTA) of the midbrain and sends dopaminergic innervation to the striatum and other limbic regions, is thought to underlie the rewarding and reinforcing properties of drugs and natural rewards. Additionally, both NK1R and NK3R influence the activity of other monoamine neurotransmitters including norepinephrine (NE) and serotonin (5HT) [19].

The neurokinins are a class of peptide signaling molecules that mediate a range of central and peripheral functions including pain processing, gastrointestinal function, stress responses, and anxiety. There are three primary neurokinin peptides, Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB). The neurokinin class of peptides is part of the tachykinin family and the associated nomenclature is influenced by this classification (see below). SP and NKA are produced by the preprotachykinin-a (PPTA) propeptide and NKB are produced by preprotachykinin-b (PPTB) propeptide. Neurokinin systems play a diverse role in physiological processes including regulation of pain processing, cardiovascular function, intestinal motility, and complex behaviors such as stress responses and drug seeking [19].

SP is a straight-chain polypeptide consisting of 11 amino acids, the first discovered neuropeptides, which plays an important role in regulating physiological functions of human body. There is abundant neurotransmitter SP in the sensory nervous system around cardiac coronary vessels. Under short-time high pressure in blood vessels, SP can dilate blood vessels, lower blood pressure, and play a protective role. From the isolated fibroblasts separated from hypertensive mouse model, researchers have found that SP could be released quickly to regulate the adhesion between cells and matrix and genes related to cellular matrix, and become involved in myocardial remodeling by binding with NK1R receptors without changing the function of fibroblasts. SP could inhibit myocardial cell apoptosis caused by norepinephrine and further block the deterioration of myocardial function [13]. Substance P (SP) is an undecapeptide member of the tachykinin family. It is produced by an array of cells, including neurons, astrocytes, microglia, epithelial and endothelial cells, and immune cells, such as T-cells, dendritic cells (DCs), and eosinophils. SP is predominantly released by neurons and exerts its biological and immunological effects through the neurokinin receptors. SP also induces an immune response and acts as a critical mediator in neuro-immune communication. It enhances lymphocytic proliferation by upregulating IL-2 expression and directly stimulates immunoglobulin production. It enhances the proliferation of bone marrow stromal cells through upregulation of the Wnt signaling pathway. Furthermore, it promotes hematopoiesis via induction of IL-1 and stem cell factors in the bone marrow stroma and the peripheral blood. SP-induced production of chemokines and adhesion molecules stimulates immune cell recruitment, further amplifying the inflammatory responses [16].

Conclusion:

The neurotransmitter serotonin (5-HT) plays a major a role in a number behavioral and psychophysiological functions such as behavioral inhibition, appetite regulation, mood, cognitive functions, thermoregulation, and addictive behaviors [9]. The structural features of the 5-HT family, in complex with various ligands and effectors provide valuable insights into their ligand recognition and downstream signaling pathways. Conserved residues within their TM domains play a crucial role in ligand binding and interaction with G proteins. Diversity in extracellular loops, particularly ECL2, suggests potential variations in ligand selectivity and receptor function among subtypes. The OBP and EBP modulate ligand selectivity and receptor function, while specific G protein coupling profiles determine intracellular responses. Additionally, arrestins' involvement adds complexity to GPCR regulation. 5-HT receptors have implications for mental health disorders and neurological diseases [3]. The pathogenesis of depression is undeniably influenced not only by the serotonergic system but also by the diversity of serotonin receptors and the intricate molecular mechanisms activated by serotonin. This complexity offers extensive opportunities for further exploration of the serotonin system's involvement in mood disorders. Moreover, it provides a foundation for the development of next-generation antidepressants with improved efficacy and faster therapeutic responses. The existing knowledge about the role of oligomeric complexes formed by 5-HT receptors in the brain indicates that these complexes serve as molecular hubs for the dynamic integration and adaptation of biological signals. These include the regulation of neurotransmitter balances, synaptic plasticity, and the modulation of behavioral and emotional responses. The imbalance between monomeric and oligomeric serotonin receptors likely plays a significant role in the pathophysiological processes leading to depressive disorders. Consequently, restoring these integrative molecular mechanisms holds promise for producing antidepressant effects and represents a compelling target in the development of new drugs for depression treatment. Such drugs might also ameliorate the delayed antidepressant effects associated with SSRIs and other existing antidepressants [5]. More research is needed to determine the potential that 5-HT has.

Over 80 years has passed since the discovery of substance P (SP), and a variety of peptides of the tachykinin (TK) family have been found and investigated. SP, neurokinin A (NKA), and neurokinin B (NKB) are representative peptides in mammalian species. SP and NKA are major excitatory neurotransmitters in the peripheral nervous system, while NKB is primarily involved in the central nervous system (CNS). Moreover, TK peptides play roles not only as neurotransmitters but also as local factors and are involved in almost all aspects of the regulation of physiological functions and pathophysiological processes. The role of SP as a mediator of pain processing and inflammation in peripheral tissues in coordination with transient receptor potential channels is well established, while novel aspects of TKs in relation to hematopoiesis, venous thromboembolism, tendinopathy, and taste perception have been clarified. In the CNS, the NKB signaling system in the hypothalamus has been shown to play a crucial role in the regulation of gonadotropin hormone secretion and the onset of puberty, and molecular biological studies have elucidated novel prophylaxic activities of TKs against neurogenic movement disorders based on their molecular structure [20].

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