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TENEURINS, TCAP, AND LATROPHILINS: ROLES IN THE ETIOLOGY OF MOOD DISORDERS

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Abstract

Mood disorders, including anxiety and depression, are thought to be characterized by disrupted neuronal synapses and altered brain plasticity. The etiology is complex, involving numerous regions of the brain, comprising a multitude of neurotransmitter and neuromodulator systems. Recently, new studies on the teneurins, an evolutionary ancient family of type II transmembrane proteins have been shown to interact with latrophilins (LPHN), a similarly phylogenetically old family of adhesion G protein-coupled receptors (GPCR) forming a trans-synaptic adhesion and ligand-receptor pair. Each of the four teneurin proteins contains bioactive sequences termed the teneurin C-terminal associated peptides (TCAP-1-4), which possess a number of neuromodulatory effects. The primary structures of the TCAP are most closely similar to the corticotropin-releasing factor (CRF) family of peptides. CRF has been implicated in a number of diverse mood disorders. Via an association with dystroglycans, synthetic TCAP-1 administration to both embryonic and primary hippocampal cultures induces long-term changes in neuronal structure, specifically increased neurite outgrowth, dendritic branching, and axon growth. Rodent models treated with TCAP-1 show reduced anxiety responses in the elevated plus-maze, open-field test, and acoustic startle test and inhibited CRF-mediated cocaine-seeking behaviour. Thus the teneurin/TCAP-latrophilin interaction may play a major role in the origin, development and treatment of mood disorders.

Keywords

• Addiction • Anxiety • Corticotropin-releasing factor • Neuromodulation • Secretin peptide family • Stress • Synaptic plasticity

1. Introduction

1.1 Etiology of mood disorders

There is a high lifetime prevalence of mood disorders among adults (approximately 21%), and this is a concerning issue, as mood disorders are associated with an increased mortality risk [1]. The clinical manifestations of mood disorders involve a change in the emotional state, and can involve anxiety, depression, or mania [2]. These changes negatively affect the cognitive functioning of the individual, are economically damaging and may contribute to a poor quality of life [3]. Thus, it is important for current research to delineate the anatomical and pharmacological pathways associated with affective disorders.

Understanding the neurobiology behind mood disorders has proven to be a considerable challenge, as there are many overlapping neural circuits and predisposing factors. For example, abnormal structural changes in both the hippocampus and amygdala are implicated in both depression and anxiety. Research shows patients with anxiety have reduced neuronal connections between emotion processing (i.e. amygdala) and emotion modulation regions (i.e. medial prefrontal cortex) [3]. In depressed patients, MacQueen *et al.* [4] found decreased hippocampal volume, and impaired explicit memory and contextual learning. It was suggested that reduced hippocampal volume might be partly due to the retraction of dendrites.

Dysregulated neurotransmitter systems are also contributors to the development of affective disorders: individuals with depression and mania show alterations in neurotransmitters such as serotonin, dopamine, γ-aminobutyric acid (GABA), and glutamate. Current pharmacological treatments have targeted the serotonin re-uptake system with monoamine oxidase inhibitors [3]. However, patients prescribed with serotonergic anti-depressants experience unwanted side effects and do not have complete symptom relief, indicating a need for improved treatments. Furthermore, individuals may be predisposed to mood disorders if they have an increased vulnerability to stress and/or have been consistently exposed to a stressful environment. Glucocorticoid hormones, as a result of corticotropin-releasing factor (CRF) secretion, become elevated during stress; and prolonged CRF signaling (i.e. chronic stress) may be detrimental to brain functioning and plasticity [2].

1.2 Role of CRF in mood disorders

CRF is expressed throughout the central nervous system, with high expression in

the limbic regions, implicating its role in the pathophysiology of depression and anxiety. As mentioned above, CRF is the main neurohormone involved in the stress response, and its behavioural effects are associated with stimulation of CRF-R1 and CRF-R2 receptors in extra-hypothalamic regions [5,6]. In particular, CRF release during stress activates neuronal projections in the limbic system, such as the basolateral nucleus of the amygdala, and has anxiogenic effects [7]. Moreover, excess CRF secretion can be detrimental to brain development and morphology, as it is shown to affect the hippocampus, a brain region involved in the glucocorticoid negative feedback circuit [4]. Specifically, hippocampal neurogenesis may be suppressed, affecting neuronal synapse formation and networks. CRF is also released in the dorsal raphe nucleus (associated with serotonergic projections) and locus coeruleus (associated with noradrenaline projections), further supporting the role of CRF in depression [8].

Evidence also shows increased cerebrospinal fluid concentrations of CRF in suicide victims, and higher numbers of CRF-producing paraventricular nucleus neurons in those with depression [9, 10]. In addition, hyperactivation of the CRF pathway leads to elevated hypothalamic CRF levels, potentially disrupting sleep, appetite, and libido [8]. Research of human CRF genetics reveals that CRF-related single nucleotide polymorphisms (SNP) may affect CRF hyperactivity and increase the vulnerability of developing depression [11]. In particular, individuals with major depression have SNP in the CRF-binding protein (CRF-BP) gene, which is involved in regulating CRF availability in the central nervous system. In terms of potential therapies, clinical studies suggest that selective CRF receptor antagonists may serve as antidepressants [7]. However, centrally administering CRF receptor antagonists in the brain appears to be anxiolytic, but with low efficacy [10].

1.3 CRF as an ancient peptide and search for progenitors of CRF

As part of a conserved peptide superfamily, CRF evolved from pre-existing early animal (metazoan) peptide genes that were subsequently evolutionarily selected by multicellular organisms to facilitate physiological and behavioural adaptations that led to the development of environmental stress-coping. After a number of gene duplication events in chordates (and hence mammals and humans), a number of CRF paralogues were formed, including the urocortin peptides (urocortin-1, urocortin-2, and urocortin-3) [12]. Also, CRF orthologues were established such as the diuretic hormone in insects, urotensin-1 in fish and sauvagine in frogs [12]. Progenitors of CRF-like peptides then developed, including calcitonin, glucagon, secretin, and pituitary adenylyl cyclase-activating peptide (PACAP) [13]. Not only do these CRF progenitor peptides share similar secondary structures, but their receptors also show structural homology (i.e. long N-terminus and seven transmembrane domains).

Another peptide that shares a similar amino acid sequence with CRF is the teneurin C-terminal associated peptide (TCAP) (Fig. 1). Found on the extracellular tip of teneurin transmembrane proteins, TCAP has about a 20% sequence similarity to CRF, and it is suggested that TCAP, CRF, and calcitonin families all share a common genomic origin [14]. Once cleaved from its proprotein, TCAP is able to exert various functions in the brain. The neurological actions of TCAP are distinct from CRF, however, and research shows that TCAP is involved in inhibiting CRF-induced stress and anxiety-related behaviours. Taken together, these studies indicate that TCAP as a bioactive peptide evolved early in metazoan ancestry and has become associated with a number of physiological systems in complex organisms such as mammals and humans.

2. Discovery of teneurins and TCAP

The first discovery of teneurins was by a group of researchers examining tenascin-related genes in *Drosophila* [15]. They initially found *Drosophila* teneurin-accessory (*ten-a*),
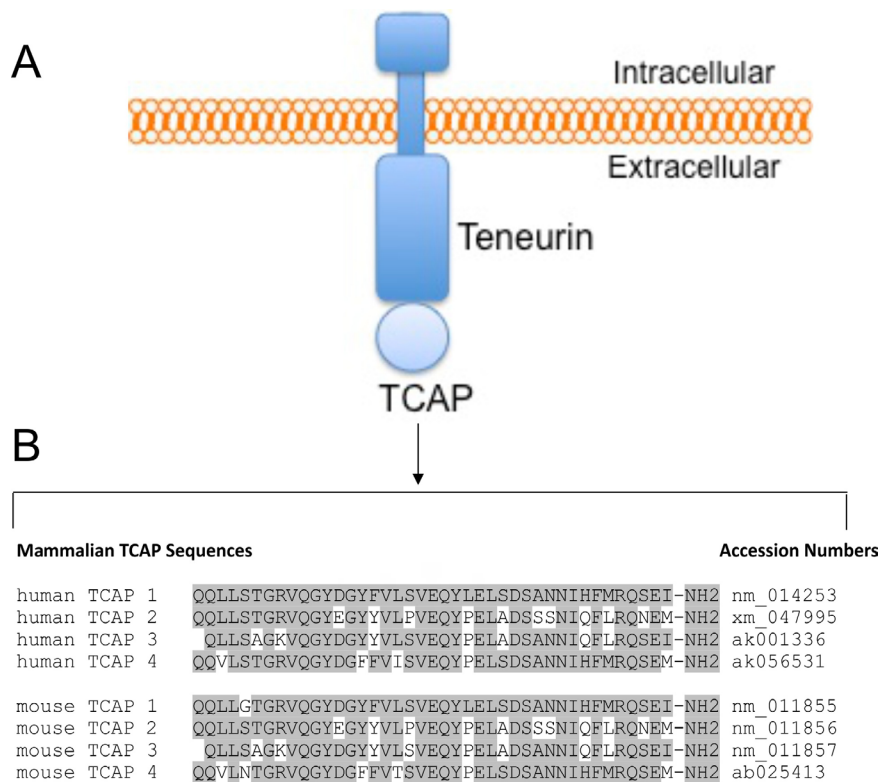

Figure 1. Structural relationship of teneurins and TCAP. A. Schematic of teneurin transmembrane protein and the extracellular region containing TCAP at the C-terminus. B. Primary structure of human and mouse TCAP. The gray regions indicate sequence identity relative to human TCAP-1. Note the high degree of conservation among the peptides.

and teneurin-major (*ten-m/Odz*) genes; and later, four teneurin paralogues (*ten-1-4*) were discovered in vertebrates [16]. Teneurins are expressed in both neural and non-neural tissues, but are most prominent in the central nervous system and during morphogenesis. For example, *ten-1-3* are found in the CA2 region of the hippocampus, and *ten-1-4* are all expressed in the dentate gyrus [17]. In addition, teneurins are involved in the development of visual, olfactory, and auditory systems [18, 19]. Teneurins exhibit a unique architecture with several functional domains, and have 300-375 and 2400 amino acids on the intracellular and extracellular domains, respectively [16]. Interestingly, there is a high similarity between extracellular, but not intracellular, teneurin domains in *Ten-a*, and *Ten-m/Odz* [17]. The last exon on the 3′ terminal end of teneurin contains a phylogenetically conserved sequence called the 'teneurin C-terminal-associated peptide (TCAP)' that can function independently from teneurin, and may be liberated by proteolytic cleavage at a furin-like site or by independent transcription [20].

TCAP is 40-41 amino acids long, and was originally discovered during the cloning of rainbow trout hypothalamic cDNA that hybridized to a mammalian *CRF*-related probe [21]. It is now known that four isoforms of TCAP (TCAP-1-4) are found on the last exon of their corresponding teneurin-1-4 genes, but are processed and expressed differently among tissue types and developmental stages [13]. However, currently, only *TCAP-1* is expressed as an mRNA separate from its associated teneurin. Using 5′-RACE PCR, a distinct *TCAP-1* mRNA was found in mouse brain [20]. The 5′ untranslated region and propeptide region are encoded within the terminal exon of the *teneurin-1* gene. However, the promoter region for this mRNA has not been identified. In addition, immunolabelling studies performed with specific antisera indicate that the majority of the teneurin-1 immunoreactivity is confined to the plasma membrane, whereas most of the TCAP-1 labelling occurs in the cytosol [20]. Taken together, this would indicate, that in some cases, TCAP-1 is likely functionally independent from teneurin-1. The peptide sequence of TCAP is highly conserved in all vertebrates:

TCAP sequences possess 73–88% sequence identity among its four human paralogues and 71–87% among mouse paralogues relative to TCAP-1 [21]. Mouse and rat TCAP are identical, whereas the similarity between human and mouse orthologues is 95–100%. There is only one amino acid difference between mouse and human TCAP-1. At position 5, a glycine residue in mouse TCAP-1 has been substituted with a serine in human TCAP-1. Human TCAP-2 and TCAP-3 are identical to mouse TCAP-2 and TCAP-3, respectively. For TCAP-4, there are two amino acid differences. In mouse TCAP-4, asparagine in position 5 and threonine in position 18 has been replaced with serine and isoleucine, respectively, in human TCAP-4. Furthermore, the TCAP family of peptides are amidated at the C-terminal end, and possess a pyroglutamyl residue in position 1 and cleavage sites, all of which are structural hallmarks of a cleavable bioactive peptide [21].

3. Structure and function of the teneurin-latrophilin complex

3.1 Discovery of latrophilins and interaction with TCAP and teneurins

Recent research suggests that TCAP forms a ligand-receptor pair with latrophilin (LPHN), an adhesion GPCR found in all vertebrates and is located on the presynaptic plasma membrane [22, 23]. The vertebrate LPHN was originally purified using α-latrotoxin (α-LTX) affinity chromatography, partially sequenced, cloned and over-expressed [24, 25]. Evidence indicates that LPHN is the receptor for the black widow spider toxin; α-LTX, and α-LTX binding stimulates exocytosis of neurotransmitters from synaptic vesicles [25]. LPHN has three known homologues (LPHN-1-3), and LPHN-1 and -3 are found almost exclusively in the brain, where LPHN-1 is more dominant in expression and is 50-fold more abundant in brain compared to other tissues [26]. Although some expression of LPHN-2 has been found in the brain, it is highly expressed in lung and liver with smaller amounts found in kidney and low expression in muscle cells [26]. LPHN-1 was shown to possess an 849-residue N-terminal domain, 7 transmembrane regions consistent with GPCR, and a 372-residue cytoplasmic tail

for a total of 1466 residues [25].

In vertebrates, all three binding domains of the LPHN are functional although they have evolved to become more specialized to vertebrate physiology. Originally identified as a rhamnose binding region, the lectin-like domain is likely more specialized to bind galactose in vertebrates. Within the three known LPHN, the highest level of sequence conservation occurs within the lectin-like domain. Also, there are a number of PEST sequences (PEST; proline, glutamic acid, serine and threonine-rich regions) that act as rapid proteolysis signals [26]. Not only are the LPHN known as the calcium-independent receptors for α-LTX (CIRL), but have also been named the Lec 1, 2 and 3 receptors within the Adhesion family of GPCRs. Lectins have been well established as carbohydrate-recognition domains that have been implicated in a number of functions including cell adhesion, cell signaling, immune responses, host-pathogen interactions and cellular growth regulation [27]. Although rhamnose has been established to have the highest affinity among carbohydrates in LPHN, rhamnose is rarely found in animals and has no biosynthetic pathway. It has been argued that rhamnose may serve an antimicrobial role, as it is present in bacterial cell walls [27]. Galactose binds this region in a similar position as rhamnose. However, both rhamnose and galactose bind to LPHN with a Kd in the millimolar range, suggesting that these carbohydrates by themselves are not the cognate ligands for this domain. Moreover, because of the numerous amino acid substitutions in the binding domain, this region may have evolved to serve protein-protein interactions as well [27].

Evidence from recent experiments indicates that the extracellular domain of LPHN interacts with teneurin/TCAP to form a trans-synaptic cell adhesion complex. The first study to identify a teneurin-LPHN interaction was by Silva *et al.* [22], who found strong binding of teneurin-2 to the lectin domain of LPHN-1 in purified rat brain. Specifically, LPHN-1 interacted with an isolated ̰275 kDa teneurin-2 splice variant (that contains TCAP-2), and the authors named this region the "LPHN-1-associated synaptic surface organizer" (Lasso). Additional experiments

using hippocampal cell cultures showed that Lasso-LPHN-1 binding occurred across synaptic junctions, and that the size of this complex is able to span the synaptic cleft [22]. Also, another study found heterophilic binding of teneurin-2 and -4, but not teneurin-1, to LPHN-1 on the cell surface of HEK (human embryonic kidney) cells [23]. Thus, these experiments point to a potential role of LPHN and teneurins/TCAP in maintaining synapses and neural integrity via a number of inter-molecular interactions.

3.2 Stoichiometry of teneurin-latrophilin complex

The architecture of the teneurin/TCAP-LPHN complex has recently been characterized, and it appears that several proteins interact at different domains (Fig. 2) [28]. As mentioned previously, postsynaptic teneurin binds to the lectin domain of LPHN domain, with nanomolar affinity. Then, on the C-terminal extracellular end of teneurin, TCAP binds to the hormone-binding domain of LPHN. In LPHN, the olfactomedin-binding region has been implicated with the binding of fibronectin leucine-rich transmembrane proteins (FLRT), whereas both the lectin and olfactomedin binding domains are required for the binding of teneurins [29]. However, where α-latrotoxin binding shows a wide expression pattern in the brain, both FLRT and teneurins show a more restricted pattern of expression suggesting that α-latrotoxin binds to additional non-LPHN sites. Interestingly, both FLRT and teneurins along with the LPHN possess sufficiently elongated and flexible extracellular domain regions to span the synaptic cleft. Thus, it is possible that a ligand-like region exists at the distal regions of the FLRT and teneurin extracellular domains [29]. In all four teneurin proteins, the TCAP region is found at the distal aspect of the extracellular domain and, therefore, is poised to act as a tethered ligand when associated with the teneurins.

Yet despite the compelling relationship of TCAP with family B ligands, we could find no clear evidence of binding and activation with known Secretin family of GPCR (unpublished observations). However, during this time, several lines of evidence emerged that the TCAP receptor may have belonged to the Adhesion class of GPCR. Moreover, the Secretin family of GPCR may have evolved directly out of the Adhesion family of GPCR [30, 31]. Interestingly, the Adhesion GPCR typically contain complex extracellular domain regions that interact with numerous associated proteins. Thus, the search for the teneurin/TCAP receptor has led to the realization that multiple extracellular and plasma membrane associated proteins may be involved. Given this consideration, TCAP show a sequence similarity among ligands that bind to the Secretin family of receptors. In general, the sequence similarity decreases between TCAP and the Secretin-family ligands as the more derived (phylogenetically younger) the ligand-receptor pair is relative to the phylogeny of the secretin family receptor member. Thus, the earliest evolving receptors, CRF and calcitonin show the greatest sequence similarity, whereas more derived (later evolving) receptor-ligand pairs show less sequence similarity (e.g. secretin, glucagon, PACAP) [23]. Taken together, these data suggest that the TCAP/teneurin receptor pairing evolved before the class B/secretin family of receptors. The relatively high level of sequence identity conservation of TCAP with respect to these ligands suggests that TCAP was an early progenitor of the family B peptides. This relationship is important as all of these ligands are associated with sensory integration and energy metabolism and furthermore suggests that TCAP peptides may have some overlapping functions with Secretin receptor family ligands [23].

3.3 Signal transduction of teneurins, TCAP and actions on cytoskeleton, relating to neurite, dendrite and axon formation

Synaptic cell-adhesion molecules are integral in establishing and maintaining synapses between neurons [23] and, therefore, play a role in signal transduction via strengthening connections between dendritic spines. The teneurin-latrophilin pair appears to be the only known trans-synaptic unit that is conserved between invertebrates and vertebrates [22]. Given the long evolutionary conservation of this complex, it is perhaps not surprising that the activation of this complex induces a number of signal transduction pathways.

The teneurins themselves appear to have an independent signaling pathway. The intracellular domain of teneurin-2, once cleaved, can translocate to the nucleus and regulate zic-1 transcriptional activity [18, 33]. However, the events triggering the release of the N-terminal fragment are not known.
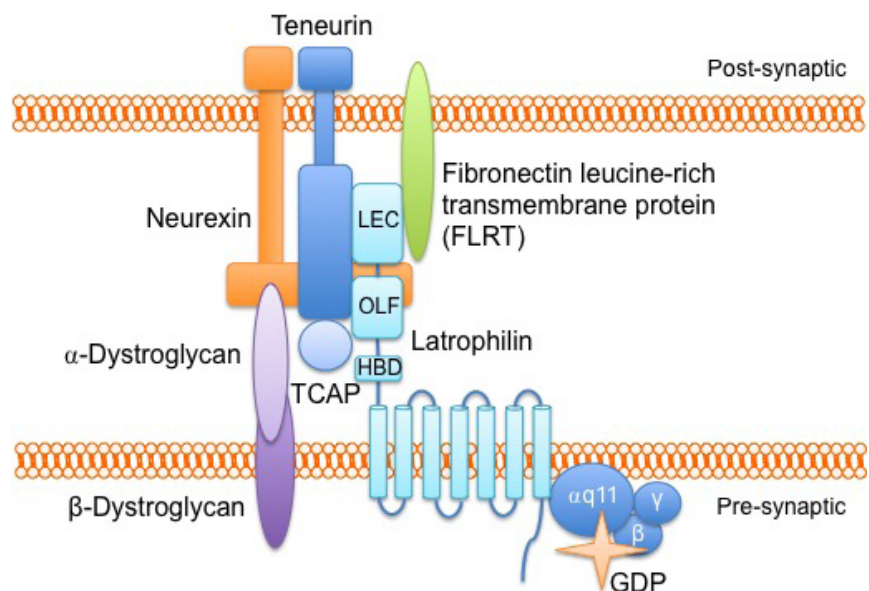

Figure 2. Schematic of trans-synaptic teneurin-latrophilin ligand-receptor complex with its affiliated stabilizing proteins, dystroglycans, neurexins and fibronectin leucine-rich transmembrane proteins (FLRT) [see reference 28].

Moreover, the mechanisms by which the developmental and trophic functions of the teneurins occur remain uncharacterized, but points to a recruitment and re-organization of cytoskeletal elements and cytoskeletal regulatory proteins.

We previously established that TCAP activates a cAMP system [21, 34], and in addition, stimulates a MEK-ERK1/2 signal cascade [35] to stimulate a number of cytosolic processes. For example, activation of the MEK-ERK1/2 pathway leads to increased cytoskeletal growth and microtubule dynamics in neuronal cells [35]. These studies also established an association of the TCAP receptor with the dystroglycans (Fig. 2) [35-37]. Thus, exogenous synthetic TCAP-1 could act through its association with LPHN causing downstream effects of the Gαq11 unit.

4. Effects of TCAP/teneurin-latrophilin interactions on mood disorder associated behaviours

4.1 Teneurin/TCAP

TCAP has been studied with emphasis on pathways related to anxiety and emotionality suggesting a role in mood disorders. The acoustic startle test is particularly useful at assessing the innate anxiety in naïve animals. When treated with intracerebroventricular (ICV) TCAP-1, high-reactive rats had a reduced acoustic startle response, whereas low-reactive rats had an increased response, indicating that TCAP may have a normalizing effect on behaviour [34]. Moreover, in a subsequent study, TCAP-1 could block the CRF-mediated action on the acoustic startle test [38]. In addition, addiction behaviours can be increased during periods of CRF-induced anxiety. When synthetic TCAP-1 was administered ICV, rats with a 3 hour-period of cocaine access showed an attenuated CRF-mediated cocaine-seeking response [39]. In another study, rats injected intravenously (IV) with TCAP-1 were subjected to either a 3-hour (short access) or 6-hour (long access) period of cocaine exposure during the reinstatement period [40]. Interestingly, in short-access rats, the lower dose of TCAP (300 pmol) was effective at blocking the CRF-induced cocaine reinstatement. However, in long-access rats, only the higher dose of TCAP (3000 pmol) was effective in ablating cocaine addiction. These findings suggest that TCAP-1 could be acting through its own receptor signaling system to mediate neuroplastic changes and inhibit CRF-driven systems. Because CRF is given exogenously to rats, TCAP-1 cannot be inhibiting the release of CRF, thus TCAP may downregulate CRF receptor expression or activity, thereby attenuating the biological actions of CRF. Such changes may involve neuroplastic regulation. Similar neuroplastic reactions were shown in findings from Tan *et al.* [41], where a TCAP-1-dependent increase in spine density in the hippocampus may reflect a homeostatic mechanism to increase the connections after synthetic TCAP-1 acted to attenuate existing synapses. In the short term, the postsynaptic regions would be expected to increase dendrite spine number to maintain the signal. Then, in the long term and under repeated TCAP-1 administration (and assuming TCAP-1 reduces neurotransmitter release) the spine density would be reduced due to continued reduction of the neurotransmitter signal. Thus, given these findings, TCAP-1 along with its teneurin-latrophilin unit may modulate the strength of interaction among particular neuronal circuits. We might postulate, therefore, that TCAP-1 action may inhibit or reduce the efficacy of strong inhibitory pathways while similarly doing the same on strong stimulatory pathways, thereby returning key learning pathways to a more basal level. Thus, in cases of addiction behaviours, or behaviours developed as a result of chronic stressors, TCAP-1 may disrupt these pathways.

Although TCAP-1 has been shown to have actions that are pertinent to the etiology of mood disorders, a number of studies indicate that the teneurin and latrophilin complex is, likewise, associated. Teneurins act, in part, to maintain neural networks by promoting synapse connectivity and increasing neurite outgrowth [42, 43]. Additionally, teneurins are integral to the normal development of visual, auditory, and olfactory pathways [43, 44]. For example, teneurin-3 is required for binocular vision, as it regulates mapping of ipsilateral axons connecting the ventral retina to the dorsal lateral geniculate nucleus [43]. Moreover, teneurin-1 is expressed prominently in the L5 and L6 regions of the neocortex [29] and in the piriform cortex, a region associated with processing of odour and pheromone signals [34]. Ultimately, teneurins are important for basic brain maturation and function, as they regulate synaptic plasticity and modulate sensory processes.

5. Conclusion

Taken together, these studies indicate that the teneurin/TCAP system is an essential component of sensory processing. Sensory regulation and integration is a key component of mood disorders. Because the length of teneurin and LPHN together can span the synaptic cleft [22], this allows teneurins to interact with adjacent neurons thus increasing efficiency of the synapse. Thus, by regulating the efficacy of this synapse, modulation of the teneurin/TCAP-latrophilin pair has the potential to regulate a number of mood disorders.

Acknowledgements

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