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Neurochemical Markers in the Mammalian Brain: Structure, Roles in Synaptic Communication, and Pharmacological Relevance

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Abstract

Background—Knowledge of molecular marker (typically protein or mRNA) expression in neural systems can provide insight to the chemical blueprint of signal processing and transmission, assist in tracking developmental or pathological progressions, and yield key information regarding potential medicinal targets. These markers are particularly relevant in the mammalian brain in light of its unsurpassed cellular diversity. Accordingly, molecular expression profiling is rapidly becoming a major approach to classify neuron types. Despite a profusion of research, however, the biological functions of molecular markers commonly used to distinguish neuron types remain incompletely understood. Furthermore, most molecular markers of mammalian neuron types are also present in other organs, therefore complicating considerations of their potential pharmacological interactions.

Objective—Here, we survey 15 prominent neurochemical markers from five categories, namely membrane transporters, calcium-binding proteins, neuropeptides, receptors, and extracellular matrix proteins, explaining their relation and relevance to synaptic communication.

Method—For each marker, we summarize fundamental structural features, cellular functionality, distributions within and outside the brain, as well as known drug effectors and mechanisms of action.

Conclusion—This essential primer thus links together the cellular complexity of the brain, the chemical properties of key molecular players in neurotransmission, and possible biomedical opportunities.

Keywords

molecular markers; membrane transporters; calcium-binding proteins; neuropeptides; receptors; extracellular matrix proteins; neuron types; drug effectors

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

1. INTRODUCTION

In this review, we define neurochemical markers as genes and proteins that are differentially expressed across distinct cell types in the central nervous system. Although knowledge of such data is far from complete, rudimentary comprehension and exploitation of molecular biodiversity has already opened many promising research avenues. The expression (or lack thereof) of molecular markers can yield information about cellular populations and shed light on both normal biological processes and pathogenic events. More specifically, seminal studies used molecular markers to (1) simultaneously classify and sub-classify assemblages of cells while providing informative signatures about their functional mechanisms [1–9]; (2) estimate direct and indirect numbers and/or densities of cellular populations [10,11]; and (3) detect and diagnose abnormal cells (e.g. cancerous tumors) or possible pathological changes in association with certain diseases [12–14]. Such insights are especially critical in the mammalian brain, where understanding of the relationships between molecular factors and higher-level cognitive functions and how diseases alter these cognitive functions is still limited.

Marker expression may be detected through various methods that depend on the type of molecule. At the pre-translational level, in situ hybridization is a prevalent method utilizing a labeled complementary DNA or RNA probe to pinpoint specific sequences in the tissue, with newer techniques like single-cell RNA sequencing gaining traction. For proteins, immunohistochemistry is widely used, a technique in which antibodies designed to interact with certain antigens are introduced into the tissue and protein binding is detected through fluorescent or color-staining reactions.

Despite the aforesaid benefits and interest, neurochemical marker research has historically confronted limitations. Perhaps most critically, widely used immunoassay approaches are technically demanding and limited to determining co-expression for only a few molecular markers at once [15]. Thus, building full molecular profiles through these methods has been cost- and time-prohibitive.

More recent experimental techniques, including several based on fluorescence, provide diverse ways of detecting ligand binding and probing intermolecular interactions. Fluorescence Resonance Energy Transfer (FRET) [16], array tomography, which offers high-throughput, high-resolution proteomic imaging of neuronal tissue [17], and Green fluorescence protein Reconstitution Across Synaptic Partners (GRASP), which allows the mapping of synaptic partners by reconstituting complementary fragments of fluorescent proteins tethered to pre- and postsynaptic neurons [18] are a few that are particularly relevant or promising.

A plethora of studies characterizes and, sometimes, relates these molecular expression products with morphological, electrophysiological, and synaptic properties in individual neurons or in a slice of brain tissue. Large-scale studies [19,20] are amassing datasets containing mRNA and protein localization information across the entire brain. In a particularly notable repository built from more than 25,000 in situ hybridization

experiments, the Allen Brain Atlas collected gene expression data for approximately 20,000 genes in the mouse brain [21].

Though we are aware of the expression of many molecular markers in the brain and other body systems, their functions are rarely well characterized. In fact, the literature is rife with expression reports for molecular markers that simply had readily available detection reagents, were easy to identify, and/or were previously cited. To make the interpretation more challenging, molecular markers are often referred to by numerous variations of names, synonyms, and abbreviations [22].

Here we present a systematic review of fifteen of the most studied neurochemical markers in the mammalian brain, focusing our discussion to rodents and, in particular, mice. We selected these specific markers in light of the significant attention they have received in seminal works on both the cerebral cortex [23,24] and the hippocampus [8,10,25,26]. In these and other brain regions, these 15 neurochemical markers have proven to be effective for identifying neuronal subpopulations and quantifying cellular architecture. Because synaptic communication is integral to neuronal function, we begin with an outline of neurotransmitters and related supporting molecules that make viable marker candidates. Then, for select neurochemical markers identified as useful in discriminating neuron types, we investigate their structures, sequences, and nomenclature, before delving into function and pathology, and, finally, pharmacological applications. We close with an overview of known relationships between these markers and neuron types in the hippocampal formation and other brain regions. Together, this information constitutes an informative primer for researchers, illuminates gaps in knowledge, and collates marker-pathology linkages that may be useful in drug targeting.

2. TYPES OF NEUROCHEMICAL MARKERS IN THE BRAIN

The primary chemical messengers in the central nervous system are neurotransmitters (NT), which transfer signals across synapses from pre-synaptic neurons to post-synaptic neurons and other targets. NTs may be classified according to their function (excitation or inhibition), action (direct or neuromodulatory) or, more discriminately, molecular structure (amino acids, monoamines, and peptides, among others). Glutamate and gamma-aminobutyric acid (GABA), two amino acids, are the most prevalent NTs in the central nervous system. Glutamate, which promotes excitatory effects by increasing the probability that the target neuron will fire an action potential, is utilized in more than 90% of cortical synapses [27–29]. It has a major role in synaptic plasticity and, thus, is implicated in cognitive functions such as learning and memory [30]. GABA, a non-standard and non-proteinogenic amino acid, is the next most prevalent NT and in the mature brain is inhibitory in most cases.

Other NTs are relatively minor in terms of overall usage in the mammalian brain, but they serve critical functions. Biogenic monoamines, including histamine, serotonin, and catecholamines (epinephrine, norepinephrine, and dopamine), regulate arousal and perception of anxiety [31], mood, appetite, and sleep [32–34], the fight-or-flight response [35], and motor control and reward-motivated behavior systems [36]. Non-monoamine NTs

include gasotransmitters (e.g. nitric oxide, carbon monoxide, and hydrogen sulfide), purines (e.g. ATP and adenosine), various peptides, and acetylcholine, which is the main effector at neuromuscular junctions [37].

The utility of neurochemical markers depends on their differential expression across neuron types. Thus, while the above NTs are fundamental in neural function, their widespread distribution renders them less practical for cellular identification. Indeed, classical NTs only constitute a small fraction of markers that viably discriminate neuron types. For instance, neuropeptides, including cholecystokinin (CCK), enkephalin (ENK), neuropeptide Y (NPY), somatostatin (SOM), and vasoactive intestinal polypeptide (VIP), all of which will be detailed in subsequent sections, are a special class of NTs that make more suitable markers. Neurons often produce one or more neuropeptides to fine-tune neuronal signaling with enduring effects (often hours to days) [38], as neuropeptides do not undergo cellular reuptake after secretion.

In addition, many proteins and genes differentially expressed in distinct neuron types pertain to the biochemical steps immediately preceding or following neurotransmission, as illustrated in Fig. 1 and overviewed below. These include vesicular packaging, transport, and fusion; calcium influx, coordination, and storage; neurotransmitter release, binding, and reuptake; ligand binding to ionotropic and metabotropic receptors; and signal or affinity modification by extracellular matrix complexes.

Prior to the arrival of an electrical action potential at a synapse, small, differentially expressed proteins called vesicular neurotransmitter transporters regulate the passage of specific NTs into vesicles, thereby determining the amount of neurotransmitter released per vesicle. Based on their substrate specificity and amino acid sequence similarity, nine vesicular transporters have been divided into three subcategories. The SLC17 gene family consists of the three vesicular glutamate transporters (vGluT1, vGluT2, and vGluT3, the last of which will be reviewed here), the vesicular excitatory amino acid transporter (VEAT), and the vesicular nucleotide transporter (VNUT). The SLC18 gene family comprises vesicular acetylcholine transporter (VACHT) and the vesicular monoamine transporters (VMAT1 and VMAT2), which pack serotonin, dopamine, noradrenaline, and histamine. Finally, the SLC32 gene family includes the vesicular GABA transporter known as VGAT [39].

In a subsequent step, an action potential depolarizes the presynaptic cell membrane resulting in an influx of Ca^{2+} into the axonal terminals through calcium channels. At this point, calcium-binding proteins (CaBP), such as calbindin (CB), calretinin (CR), and parvalbumin (PV), all useful markers that are detailed below, bind to the ions, thereby regulating intracellular calcium levels. When calcium reaches sufficiently high concentrations, the NT-containing vesicles fuse with the synaptic membrane expelling their contents into the synaptic cleft via exocytosis. Neurotransmitters then seek to bind specific receptors that are themselves differentially expressed on post-synaptic cells.

AMPA, NMDA, and kainate are ionotropic receptors (i.e. transmembrane ion channels that open or close in response to the binding of a NT and tend to mediate fast synaptic transmission) for glutamate, allowing the passage of Na^+ , K^+ , and/or Ca^{2+} . In contrast,

metabotropic glutamate receptors use slower, cascading signal transduction (i.e. second messenger) mechanisms, often G proteins, to activate a series of post-synaptic intracellular events. They are classified into eight types (mGluR1-8) belonging to three families according to their location, preferred agonists and activators, and function [40]. Group 1, comprised of mGluR1 and mGluR5, primarily operates on the post-synaptic side of the cleft, whereas receptors belonging to groups 2 and 3 are primarily pre-synaptic [41]. The splice variant known as mGluR1a is described below.

GABA receptors are divided into two classes: the ionotropic GABA_A (along with the GABA_{A-p} subclass, formerly known as GABA_C), allowing transmembrane Cl⁻ influx, which typically causes post-synaptic hyperpolarization, and metabotropic GABA_B. The primary type of GABA_A receptors (the “non-rho” subclass) are pentameric and usually composed of various alpha, beta, and gamma subunits, though delta, epsilon, theta, and rho may also be present [42]. The various GABA_A subunits are themselves differentially expressed, and GABA_{Aα1} is detailed below.

The affinity of receptors for NTs may be modified by extracellular matrix proteins, including reelin (RLN) [43], another molecular marker detailed below.

Finally, after vesicle release and resultant post-synaptic effects, membrane-bound transporters participate in the reuptake of some NTs back into the pre-synaptic axon. These proteins, like the vesicular transporters, are specialized to carry specific NTs, including glutamate and aspartate (excitatory amino acid transporters, or EAAT1-5), GABA (GAT1-3), and monoamines such as dopamine (DAT), norepinephrine (NET), and serotonin (SERT).

3. IDENTIFYING FEATURES AND FUNCTIONAL ROLES OF MAJOR NEUROCHEMICAL MARKERS

In the following sections, we review 15 neurochemical markers frequently utilized for their differential expression among neuron types from the five categories mentioned above: membrane transporters (vGluT3), CaBP (CB, CR, and PV), neuropeptides (CCK, ENK, NPY, SOM, and VIP), NT receptors (mGluR1a, GABA_{Aα1}, serotonin receptor 3 or “5-HT3”, cannabinoid receptor 1, and substance P receptor), and extracellular matrix proteins (RLN).

Each sub-section discusses the markers’ nomenclature and basic chemical properties (also see Table 1). Structural information was obtained from the UniProt.org knowledge base and the RCSB.org protein data bank. Hydropathy scores are calculated based on the “GRAVY” (GRand AVerage of hYdropathy) methodology, wherein the values of each residue are added and the sum is divided by the length of the sequence; scores below 0 are more likely hydrophilic, while scores above 0 are more likely hydrophobic [44]. Within every sub-section, we then describe the physiological, developmental, and pathological roles of the neurochemical markers in the central nervous system (summarized in Table 2). Additionally, we also note the presence and functionality of these markers in peripheral (neuronal and non-neuronal) systems, which may affect pharmacological interactions. These are also the

tissues where many of the markers were first discovered, most notably in the digestive and/or endocrine systems (Fig. 2).

3.1 Membrane Transporters

vGluT3, formally known as solute carrier family 17 member 8, is encoded by the SLC17A8 gene. It is a synaptic vesicle membrane protein with both the amino- and carboxy-termini located in the cytoplasm, bracketing 12 transmembrane domains that weave into and out of the vesicle. The amino acid sequence results in a net hydrophobic protein, but the cytosolic and vesicular domains are generally hydrophilic. The chain consists of 601 amino acids (aa) with a mass of 66.1 kDa.

In contrast with the more ubiquitous vGluT1 and vGluT2, vGluT3 is expressed at rather low levels in the brain. Nevertheless, certain neurons utilize the molecule to package glutamate. Interestingly, vGluT3 is occasionally co-expressed with GABA (e.g. by CCK+ basket cells in the hippocampus), suggesting a co-release of GABA and glutamate into the synapse and an important role for glutamate in the signaling of non-glutamatergic neurons [45]. In peripheral body systems, vGluT3 plays an unknown role but is expressed in the liver and kidney [46].

During postnatal development, vGluT3 is released transiently at certain locations, including in selected migrating cells and in cerebellar Purkinje neurons [47]. In the rat, between P1 and P15, vGluT3 is expressed in striatum, accumbens, hippocampus, as well as in certain caudal brain structures, including the colliculi, pons and cerebellum. During a second phase extending from P15 to adulthood, the labeling in the caudal brain fades away.

Clinically, the gene that encodes for vGluT3 has been linked to nonsyndromic, slowly progressive, hearing impairment. Though originally identified in a human molecular genetics study [48], the effect has been studied with a rodent model: SLC17A8-null mice missing the vGluT3 protein are deaf due to lack of glutamate release from hair cells at the first synapse of the auditory pathway [49].

3.2 Calcium-Binding Proteins

A family of CaBP, including the three markers discussed here, contains EF-hand domains. This structural motif has a high affinity for Ca^{2+} ions and, accordingly, the molecules undertake a crucial role in intracellular calcium homeostasis. Calbindin D28K and calretinin (CR), which is somewhat confusingly also designated as 29 kDa calbindin, are closely related proteins. The two sequences are quite similar, to the extent that CR shares 60% identical residues with CB (with 76% like or similar residues and only 2% gaps). CR is the slightly longer (271 aa versus 261) and heavier of the two and contains 6 EF-hand domains that are home to 6 Ca^{2+} -binding sites. CB contains 6 EF-hand domains but only 4 binding sites, as potential binding sites II and VI have lost their affinity for calcium [50]. A third CaBP, PV, formally known as parvalbumin alpha, is less than half the length (110 aa) of the other two and only contains two EF-hand domains and Ca^{2+} -binding sites.

Among the many CaBP in the brain, these three are particularly useful neurochemical markers due to their abundancy and variable distributions. In general, CB, CR, and PV are

segregated and rarely co-expressed, though they are frequently co-expressed with GABA [51]. Because high Ca^{2+} levels trigger exocytosis, calcium-binding proteins play a major part in modulating and mediating NT release into the synaptic cleft. The effects could be manifested as modulation of action potential duration, promotion of neuronal “bursting” (by inhibiting Ca^{2+} -dependent K^{+} currents), or as protection against excessive calcium influx that could damage the cell during prolonged periods of high activity [51,52]. In addition, CR modulates neuronal excitability by inducing long-term potentiation [53].

Also expressed in non-neuronal tissues, CB was first discovered in cytosolic fractions of the chicken intestine [54,55]. It was originally described as vitamin D-dependent because levels were diminished in vitamin D-deficient animals, but expression could be induced by treatment with vitamin D metabolites such as calcitriol [54]. In the brain, however, its synthesis is independent of vitamin D. CB has also been found in the mammalian pancreas [56], kidney [57–59], and osteoblasts, where it regulates apoptosis and serves as a critical determinant in the rate of bone formation [60]. Though CR is expressed in other parts of the body, including the lung mesothelium, urogenital tract, and adrenal gland [61], it is primarily and abundantly expressed in nervous tissue of the brain, the retina (hence its name) [62], and in sensory pathways (e.g. certain cells and fibers of the cochlear nuclei and olfactory bulb) [63]. PV is localized at high levels in fast-contracting muscles, where it assists in the contraction-regulation cycle by playing a role in Ca^{2+} exchange between the sarcoplasmic reticulum and the myofibrils [64].

During development, these CaBPs regulate Ca^{2+} pools critical for synaptic plasticity, and the first expression of all three in the brain seems to be stage-dependent. CB expression is detected before the other two, shortly after cessation of mitosis when neurons begin migration and differentiation, followed by PV, which is expressed in parallel with an increase in neuronal activity; CR is generally detected later [65].

These three CaBPs have also been linked to various neurodegenerative diseases. However, because of their very wide distribution, altered expression patterns under pathological conditions do not necessarily imply a causal relation. In particular, CB has been associated with Alzheimer’s disease. CB expression is reduced in the brains of mice and humans with Alzheimer’s [66], and removal of CB from amyloid-precursor-protein transgenic mice aggravates Alzheimer’s dysfunction [67]. Similarly, in Huntington’s disease, immunohistochemistry showed a substantial loss of CB-containing neurons from the neostriatum. This population of neurons is particularly damaged in Huntington’s, suggesting that a failure of calcium buffering or homeostasis may contribute to cell death in this pathology [68]. CB may also confer some protection to substantia nigra dopaminergic neurons against Parkinson’s disease [69]. CR, too, is a diagnostic marker for diseases, including Hirschsprung disease, where CR is absent from nerve trunks in the bowel [70], and mesothelioma, where it can help differentiate benign and malignant lung tumors [71]. In addition, loss of CR expression in hippocampal interneurons has been reported in temporal lobe epilepsy [72]. Lastly, PV expression is diminished in interneurons of individuals with schizophrenia [73]. Moreover, PV-expressing neurons are particularly vulnerable in Creutzfeldt-Jakob disease [74].

3.3 Neuropeptides

Peptides are cleaved from protein precursors, or pro-peptides, as post-translational modifications. Both the precursor and the peptide may serve as molecular markers. Table 1 provides information for the pro-peptide form of the neuropeptides for comparison purposes. These peptides are all hydrophilic.

Pro-CCK, a 115-residue chain, is cleaved into three CCK peptides with 32, 12, and 8 residues, respectively, which act on two receptors (CCK-A and CCK-B) [45]. CCK often acts as a modulator of the effects of classical neurotransmitters, including dopamine [75] and serotonin [76]. In inhibitory hippocampal basket cells, in coordination with vGluT3, CCK stimulates exocytosis of glutamate [45,77,78]. CCK also increases GABA release in the rat cortex and neostriatum [79–82]. In addition, CCK may regulate anxiety [83,84] and memory [85]. In the digestive system, in response to food ingestion, CCK induces gall bladder contraction and release of pancreatic enzymes and gastric acid, which catalyze digestion of fat, protein, and carbohydrates [86]. The peptide also plays a role in hunger suppression [87]. Pathologically, CCK has been implicated as a cause of visual hallucinations in Parkinson's disease [88]; in the digestive system, colorectal carcinomas express CCK and its receptors [89].

The enkephalin precursor is formally known as proenkephalin, proenkephalin-1, or proenkephalin-A. Its 268 aa-chain is cleaved into 8 active peptides, including two pentapeptides known as met-enkephalin (Tyr-Gly-Gly-Phe-Met) and leu-enkephalin (Tyr-Gly-Gly-Phe-Leu). Upon cleavage, each proenkephalin-A can generate four copies of met-enkephalin (from positions 100–104; 107–111; 136–140; and 210–214) and a single copy of leu-enkephalin (231–235). Both met- and leu-enkephalin bind to opioid receptors. Met-enkephalin acts through μ - and δ -opioid receptors, and leu-enkephalin acts solely through δ -opioid receptors, which are expressed differentially throughout the brain [90]. In either case, consonant with the mimicking and magnified effects of opiate drugs (e.g. morphine), the primary function of enkephalins is to modulate information related to pain perception, analgesia, and pleasure, along with responses to stress, aggression, and dominance [90,91]. Though δ -opioid receptors are restricted to the brain, μ -opioid receptors are also found in the digestive tract, where enkephalin is known to be expressed in peripheral nerves innervating enteric tissue [92]. Additionally, in the immune system, T and B lymphocytes, monocytes, and macrophages in inflamed tissue have been shown to express enkephalin [93–95]. In development, endogenous opioids serve as inhibitory growth factors limiting cell proliferation (specifically, cerebellar neurogenesis and gliogenesis) [96]. Clinically, enkephalin is a factor in drug addiction and in stimulation of the reward system: rats work for enkephalin injections delivered directly into their brains [97]. Enkephalin has also been linked to epileptic seizures [98].

Pro-neuropeptide tyrosine, pro-NPY, is the shortest and lightest of the precursors reviewed here (97 aa). It is processed into two chains: the 36-residue length NPY and the 30-residue C-flanking peptide of NPY. NPY receptors are metabotropic and have five subtypes [99]. In the central nervous system, NPY acts primarily as a regulator of energy homeostasis [100]. It is also localized to the nerves of the heart, spleen, kidney, respiratory and urogenital tracts, around blood vessels, and within visceral smooth muscle [101]. Elsewhere, increased NPY

activity has been directly tied to food intake, and it is a very potent appetite stimulant. Specifically, administration of NPY agonists increases food intake, while blocking NPY receptors decreases intake [102–104]. Furthermore, NPY concentrations are altered in both anorexia and bulimia [105], as well as in obesity [106], suggesting a key role in eating behaviors. Additional evidence in mice indicates that NPY might protect against alcoholism [107] (reviewed in [108]).

Pro-somatostatin is a 116-residue molecule that is processed into three chains: antrin, somatostatin-28, and somatostatin-14, these latter two coinciding with the C-terminus of the precursor. SOM binds to five different receptor subtypes [109]. In the central nervous system, it is particularly expressed in the hippocampal formation and the neocortex, where it has been implicated in a variety of functions, such as pain perception [110] and memory formation [111] via changes in neuroplasticity [112,113] (see [114] for review). In the hippocampus, SOM is co-released with GABA from some interneurons [25,26], and both excites and inhibits cortical neurons in tissue culture [115]. In addition, SOM was first identified in the hypothalamus, where it links the central nervous system with the endocrine system and regulates growth hormone secretion from cells of the anterior pituitary gland [116]. SOM also acts as a modulator of motor activity in the gastrointestinal tract [117]. Altered levels of SOM are observed in several brain dysfunctions, including Alzheimer's [118–121], Parkinson's [122,123], and multiple sclerosis [124]. Moreover, a near complete loss of SOM-containing neurons was observed in temporal lobe epilepsy [125,126].

Finally, the VIP encoding protein is 170 residues long and gives rise to three chains: intestinal peptide PHI-42 and intestinal peptide PHI-27, which overlap, and VIP (28 aa). Two seven-transmembrane G protein-coupled receptors are bound by VIP in the brain. VIP primarily is expressed in subsets of GABAergic interneurons [26,127], where it serves several functions. It stimulates local metabolism through glycogenolysis, which results in increased glucose availability [128]. Secondly, VIP provides neuroprotection against cell death and neurodegenerative diseases such as Alzheimer's and Parkinson's [129,130]. Thirdly, VIP+ neurons regulate circadian rhythms in the suprachiasmatic nucleus by producing higher firing rates during the day relative to night [131,132]. As its full name implies, VIP was discovered outside the central nervous system due to its role in digestion. Specifically, it induces smooth muscle relaxation to increase motility in the esophagus, stomach, gallbladder, and intestinal lumen, where it also regulates secretion of gastric acid, water, and electrolytes [133,134]. In addition, VIP is widely expressed in peripheral nerves that innervate the cardiovascular, respiratory, and reproductive systems, as well as in kidney and blood cells (Table 2) (see [135] for review). During development, VIP can stimulate neurogenesis, modulate the development of the neural tube, and affect proliferation of precursors of the cerebral cortex [136]. In fact, defects in the VIP regulation system in mice cause failure of neural tube closure and death by embryonic day 9 [137]. VIP also has proliferative activity on neural precursor cells during mice embryonic development by shortening the G1 and S phases of the cell cycle [138]. During embryogenesis, dysregulation of VIP negatively impacts neurodevelopment and has been linked to autism, Down syndrome, and fetal alcohol syndrome [139]. Lastly, VIP is involved in epilepsy [140,141].

3.4 NT Receptors

mGluR1 is a 1,199 aa-long membrane-bound protein with an extracellular domain beginning at the N-terminus and stretching 572 residues; this portion contains the five glutamate binding sites. Seven helical transmembrane domains are then followed by a long, cytoplasmic C-terminal domain. Both the extracellular and the cytoplasmic domains are hydrophilic, but the transmembrane portions lead to a slightly hydrophobic GRAVY score overall.

mGluR1a is distributed widely throughout the brain, though, unlike its ligand glutamate, not ubiquitously. As a metabotropic receptor, mGluR1 helps regulate ion channels and cell excitability [142] through secondary messenger cascades whose complex signaling pathways go beyond the scope of this review. On the pre-synaptic side of the synapse, mGluR1 acts as autoreceptor by regulating synaptic transmission and inhibiting further glutamate release [143]. Finally, mGluR1a is implicated in synaptic mechanisms of memory and learning in the cerebellar cortex [144], hippocampus [145,146] (where its function was first discovered [147]), striatum [148], and visual cortex [149].

mGluR1 receptors also have widespread distribution outside the brain, including in peripheral sensory cells, the gastrointestinal tract (or possibly in the myenteric ganglia and plexa of the enteric nervous system), adrenal gland, thymus, osteocytes, and heart [150–154]. Though mGluR1 mRNA expression increases during postnatal life, unlike mGluR3 and mGluR5, mGluR1 plays a minimal role during synaptogenesis but a large role in mature synaptic transmission [155]. Neuropathologically, mGluR1 has been linked to Huntington's disease [156] and multiple sclerosis [157,158]. In the periphery, dysfunction of the receptor has a role in ulcer formation [159] and the pathogenesis of melanoma [160].

The GABA_A heteropentamer usually is formed by alpha, beta, and gamma polypeptides in a 2:2:1 ratio [161], though in some cases other subunits such as epsilon or delta may replace gamma. The subunits arrange themselves around a central Cl⁻ conduction pore. The most common GABA_A receptor is the $\alpha 1\beta 2\gamma 2$ subtype, which accounts for 60% of all GABA_A receptors, followed by $\alpha 2\beta 3\gamma 2$ (15–20%) and $\alpha 3\beta 1\gamma 2$ (10–15%) [162]. The $\alpha 1$ subunit described here is a major molecular marker in the mammalian brain. It has a 223 aa-long extracellular ligand-binding domain near the N-terminus, three hydrophobic transmembrane helical regions that form the ionic channel, a cytoplasmic domain, and a fourth transmembrane helical region at the C-terminal of the sequence.

GABA receptors are present in most neurons in the adult brain, typically converting GABA signals into inhibitory hyperpolarization [163]. The heterogeneity afforded by their constituent subunits is a key factor in fine-tuning inhibitory transmission under physiological and pathological conditions. Specifically, GABA_A $\alpha 1$ subunit agonists potentiate inhibitory post-synaptic current amplitude to various extents depending on the degree of receptor occupancy [164]. In the hippocampus, CA1 pyramidal cells receive information from two types of CA1 basket cells through different GABA_A receptor subunits [165,166]. Specifically, synapses made with PV-expressing, fast-spiking basket cells employ the $\alpha 1$ subtype, while those made with CCK-expressing regular spiking basket cells [167] employ the $\alpha 2$.

The GABA_Aα1 receptor has been identified in peripheral tissues such as the adrenal gland, gonads, and small intestine [168,169]. Although GABA has also been detected in several additional systems and organs, much of the evidence is not specific to the subunits of GABA_A. In development, the α1 subunit displays weak expression in the cortex, thalamus, hippocampus, and cerebellum as early as embryonic day 18. Adult involvement in neurological and psychiatric diseases includes Huntington's, epilepsy, anxiety disorders, alcoholism, Angelman syndrome, and schizophrenia [170].

5-HT₃ is one of several receptors for 5-hydroxytryptamine (serotonin). It is a ligand-gated ion channel, permeable to various cations. Its activation results in fast post-synaptic depolarization. Isoform A, the canonical sequence, is 487 aa long. Much like GABA_Aα1, 5-HT_{3A} has a long extracellular region for NT binding, three transmembrane helices, a cytoplasmic domain, and a fourth transmembrane region, and, overall, is hydrophobic.

5-HT₃ receptors bind serotonin and regulate the release and effects of other neurotransmitters, both pre- and post-synaptically [171]. They have highest expression in the brainstem [172] with lower levels detected in several areas of the forebrain, where they mediate fast excitatory synaptic transmission [173–176]. In the hippocampus, antagonist blockage of 5-HT₃ receptors reduces hyperpolarization thereby enhancing both the frequency of the naturally occurring theta rhythm and the induction of long-term potentiation, resulting in improved memory [177]. Similarly, 5-HT₃ receptors modulate dopamine: agonists increase dopamine release in the striatum [178,179] and antagonists have anti-dopaminergic effects [180]. Antagonists also temper the psychomotor stimulant effects of drugs such as cocaine, amphetamines, nicotine, and morphine [181]. Peripheral roles for the receptor are less well known but, in nerves extending to the digestive system, 5-HT₃ receptors mediate signaling from the gut to the brain, including messages of nausea, pain, and bloating [182].

Cannabinoid receptors (CB1 and CB2) are metabotropic effectors activated by natural, plant-based (cannabis), synthetic, or endogenous cannabinoids [183,184]. Cannabinoid receptor 1 has seven transmembrane regions rendering it a net hydrophobic molecule. CB1 is found mainly in the brain, with high levels in the basal ganglia, hippocampus, cerebellum, and cerebral cortex, and lower levels in the hypothalamus [185,186]. This receptor is often localized to axon terminals (e.g. in CCK-positive interneurons of the hippocampus and amygdala), and its activation leads to inhibition of NT release [187–189]. This pre-synaptic action also entails a retrograde messenger role: by releasing endogenous cannabinoids, post-synaptic neurons modulate their own GABAergic inputs (an effect known as depolarization-induced suppression of inhibition [190,191]). CB1 receptors are also present in peripheral tissues, including spleen, white blood cells, heart, and gonads [192]. Pathologically, CB1 mediates most psychoactive properties of cannabis [193]; increased binding levels have been detected in schizophrenia [194] and Parkinson's [195], though this may be a side effect of treatment medications.

The substance P receptor (sub P rec) is also known as the neurokinin 1 (NK1) receptor (NK2 and NK3 receptors bind preferentially to substance K and neuromedin K, respectively). Of the receptors reviewed here, sub P rec has the shortest extracellular domain (32 aa) and is the

only one with a longer cytoplasmic domain (74 residues) than extracellular domain; in between, it has seven transmembrane regions.

As substance P is widely implicated in pain perception, inflammatory response, and stress response, antagonists that act on its receptors negate these effects [197–202]. In peripheral tissues, sub P rec are found in the digestive system [203] and endocrine glands, where they reduce levels of hormones produced in response to stress upon binding of substance P [204]. During development in the rat, the density of sub P rec is maximal one day before birth. These high levels gradually decrease until they reach adult levels two weeks after birth, suggesting an important but as-yet-uncharacterized role for substance P in the early organization of the central nervous system [205]. Pathologically, sub P rec is chiefly involved in chronic pain perception [199]. In addition, administration of specific antagonists reduces weight gain and circulating levels of insulin and leptin after a high-fat diet, pointing to a role for sub P rec in obesity [206].

3.5 Extracellular Matrix Proteins

RLN, sometimes referred to as the reeler protein, is the longest and heaviest molecular marker reviewed here by nearly a factor of three. It is encoded by the *Reln* gene, which is disrupted in reeler mice, giving them a distinctive gait and the protein its name. Structurally, the N-terminal has a 27-aa signaling peptide, a “reeler” domain with unknown function, and eight “reelin repeats” that are 300–350 aa long. These repeats have an epidermal growth-factor motif at their center that divides each repeat into two sub-repeats, referred to as A (the BNR/Asp-box repeat) and B (the EGF-like domain). Despite this interlude, the two subdomains make direct contact, resulting in a compact, but massive, overall structure with 3,461 aa.

In the central nervous system, reelin plays a pivotal role in deploying and positioning neurons during development, especially in laminated brain regions such as the neocortex, hippocampus, and cerebellum. After a multi-step synthesis involving the rough endoplasmic reticulum and Golgi vesicles, reelin is secreted through porosomes into the extracellular matrix. As young neurons migrate from the site of their origin to their final destinations, reelin binds to their transmembrane lipoprotein receptors [207,208]. This triggers a complex intracellular signaling cascade through the cytoplasm and nucleus that instructs the neurons to occupy their proper locations in the developing brain [209].

In the cortex, transient reelin-expressing cells are primarily found in the marginal zone and in the temporary sub-pial granular layer [210,211]. In the hippocampus, Cajal-Retzius cells secrete reelin into the extra-cellular matrix of the stratum lacunosum-moleculare and the outer molecular layer of the dentate gyrus [212,213]. Reelin is also expressed in the external granule cell layer of the cerebellum, where granule cell migration to the internal granule cell layer is initiated [214].

Synthesis of reelin decreases postnatally, becoming more diffuse compared to the distinctly laminar expression in the developing brain. However, in the adult, the protein still plays a role at active neurogenesis sites, including the subventricular zone and the dentate gyrus [215], and it is secreted in adulthood by GABAergic neurons that originate in the caudal

ganglionic eminence [216]. Furthermore, in the mature brain, the reelin receptor Apoer2 modulates synaptic plasticity to maintain long-term potentiation and favor memory formation [43].

Reelin expression in the brain is well documented, but a large body of evidence now suggests reelin involvement in the cellular migration and proliferation of non-neuronal tissues [217]. Reelin mRNA is found in the small intestine, where the epithelium has a high turnover rate and is subject to rapid renewal [218]; reelin is also involved in the processes of osteogenesis and dentinogenesis [219,220]. Moreover, reelin is expressed in hepatic stellate cells of the liver, an organ that is self-regenerative [221,222], along with the blood [221,223], mammary gland [224], and the bovine and chicken endometrium and ovarian follicle [225,226]. Though its exact mechanisms of action in these widespread systems are unclear, the pervasive nature of reelin, despite its large size and the energy required to secrete it, points to a broad but significant role in the development of a diverse set of organs and tissues.

Finally, regarding the pathological roles of reelin, the processes involved in tumorigenesis often employ the same pathways that are required for normal development. Thus, it is unsurprising that reelin up- or down-regulation has been implicated in many cancers. Reelin expression is reduced in hepatocellular carcinoma and breast, gastric, and pancreatic cancers [227–230]. In contrast, upregulation is observed in esophageal carcinoma, prostate cancer, and retinoblastoma [231–233]. In addition, reelin has been linked with several brain disorders, including schizophrenia [234–236], bipolar disorder [237], and Alzheimer's disease [238–240].

4. PHARMACOLOGICAL IMPLICATIONS

The documented pathological roles of nearly all molecular markers, coupled with the increasing availability of Cre transgenic mouse lines for drug testing, would suggest ample opportunities for pharmacological exploration. Surprisingly, for the 15 markers reviewed here, current prospects appear to be largely restricted to the receptors of neuropeptides and NT (Table 3). Per the drug-gene interaction database (dgidb.org) [246,247], neither vGluT3 nor any of the CaBP are known to be targeted or affected by any drug in current clinical usage. Moreover, ongoing drug development strategies do not presently focus on intervention at the calcium-regulation level. In the case of CaBP, though CB can protect cells against amyloid- β peptide toxicity [248], agents affecting intracellular calcium were of limited value in the treatment of Alzheimer's and dementia [249,250].

Similarly, drugs are not used to target directly any of the neuropeptides discussed here. However, given the wealth of preclinical data supporting the role of neuropeptides in modulating behavior, pharmaceutical companies have been attempting to target neuropeptide receptors for over two decades. Thus far, though, clinical studies with synthetic neuropeptide ligands have been unable to confirm the promise predicted by studies in animal models [251]. For each neurochemical marker in this category, Table 3 lists the human genes that encode its various receptors. Queries leveraging the DGI-DB were then run, and the number of hits for each gene was noted. From the results that met our "high-quality" threshold (i.e.

those having DGI-DB scores ≥ 5 , calculated based on number of source databases with information and the amount of supporting evidence from PubMed), a sampling of drugs was included in Table 3. They were chosen to represent the range of drug indications and interaction types (e.g. agonist, antagonist, etc.) based on available information in the PubChem database. Not surprisingly, the δ - and μ -opioid receptors are the most popular targets by a considerable margin. These receptors, to which ENK also binds, play a major role in pain perception and treatment. Receptors for other neuropeptides appear currently to be in limited pharmacological use and, when they are utilized, it is in treatment relating to digestive distress or obesity.

In contrast to the neuropeptides, four out of the five classical NT receptors we reviewed are major pharmacological targets, including GABA_A α_1 , 5-HT₃, CB₁, and sub P rec. DGI-DB searches reveal a plethora of chemicals that target these molecules to treat a variety of conditions. In particular, GABA_A receptors represent a major site of action for clinically important drugs, including benzodiazepines, barbiturates, and some general anesthetics, as well as drugs of abuse such as ethanol (Table 3 and references therein).

However, for all the analyzed targets, current indications are almost exclusively for peripheral tissue maladies. The only exception is Dronabinol, a Cannabis-derived psychoactive CB₁ ligand used in Alzheimer's patients who refuse food and exhibit "disturbed behavior". Thus, though the viability of many of these markers as drug targets remains to be seen, the field would seem quite open.

5. RELATIONSHIP BETWEEN NEUROCHEMICAL MARKERS AND NEURON TYPES

The Allen Brain Mouse Atlas (mouse.brain-map.org) is a publicly available online repository of in situ hybridization expression data for more than 20,000 genes [21]. To corroborate and extend the neurochemical patterns reviewed here, we mined the data from the main series of coronal sections from adult (56-day old) male C57BL/6J animals. For the 15 genes of the markers reported here, we extracted expression energy values (i.e. the sum of the intensity of expressing pixels in a voxel or structure divided by the number of all pixels within that same structure) for 2,493 neuroanatomical regions according to the hierarchical organization of the Allen Atlas. For the purposes of this review, we report on twelve high-level brain structures of broad interest (Fig. 3A). The full source dataset is provided (hippocampome.org/WholeBrainGeneExp) for detailed investigation within areas of more specific interest.

Expression varies for the majority of the neurochemical marker precursors of interest. As expected, the CaBP and receptors of GABA and glutamate are widely and highly expressed. The same holds for CCK, ENK, CB₁, and RLN. For other markers (e.g. the precursors of VIP, vGluT₃, and 5-HT₃, and sub P rec), intensities are quite weak at the region level. VIP data from the Allen Brain Atlas largely agrees with the literature: as a previous report [127] indicated, its receptors are particularly expressed in regions involved in learned behaviors, including the hippocampus, cortex, amygdala, and hypothalamus, but largely absent elsewhere. Also in concordance with atlas data, in situ hybridization signals for vGluT₃ in

the medial septum and basal forebrain were previously reported to be absent [273,274]. In fact, the vGluT3 (and sub P rec) precursor displays minimal regional expression outside of the striatum, and Htr3a, the gene that codes for 5-HT3, is not detected at a meaningful level in any of the regions.

Nevertheless, even in the cases of markers with little to no expression at the regional level, certain cell populations within these areas are known to express the markers. For instance, vGluT3 is expressed by localized cells in multiple brain regions, including serotonergic neurons in the dorsal raphe, cholinergic interneurons in the striatum, and certain GABAergic interneurons in the hippocampus and the cortex [45,46,273–275]. Similarly, sub P rec is expressed to some degree in superficial layers of the cortex, thalamus, hypothalamus, hippocampus, and various midbrain and hindbrain structures [196]. 5-HT3 has been detected in limited sub-populations of several regions, including the hippocampus, nucleus accumbens, putamen, caudate nucleus, amygdala, and visual cortex [173–176].

Neuron type identities can sometimes be inferred from higher-level data when anatomical parcels are predominantly and densely packed with a single type. This is the case for the principal cell layers of the hippocampus, including the granule layer of dentate gyrus and the pyramidal layers of CA1, CA2, and CA3 [276, in press]. However, in most cases, molecular expression data exists with no cell type resolution. Obtaining and reconstructing morphological information beyond the location (and shape and size) of the somata require separate, low-throughput experiments. Such assays have been performed on many well-studied neuron types (most notably in the hippocampus), but this is the exception rather than the rule. To gather this data, we combed the literature for agreed-upon evidence of expression or non-expression for the 15 markers of interest in 42 well-known neuron types in seven brain regions (Fig. 3B). Even in this dataset of familiar types and markers, expression is unknown for 70% of cases (440/630). Of the remainder, 16% (101) of the knowledge represented positive expression and a comparable 14% (89) reported negative expression, lending support to the selection of these neurochemical markers as optimally informative.

Because of the large number of molecules that often work in concert, no specific type of neuron can be fully defined by a single marker. However, certain interneuron types reliably express a given molecule across regions of the brain. For example, some perisomatic-targeting cells, like axo-axonic cells and fast-spiking basket cells, are consistently PV-positive, regular spiking basket cells typically are CCK-positive, neurogliaform cells usually express NPY, and Cajal-Retzius cells are positive for reelin.

Furthermore, certain neuron types express specific combinations of different molecular markers that can aid in their identification. For example, though interneuron-specific interneurons in CA1 of the hippocampus display a variety of morphologies and inhibit distinct sets of interneurons, they resolutely express CR and VIP [277,278]. In the amygdala, in addition to confirming the perisomatic-targeting type expression data mentioned above [279], neurogliaform cells express NPY as well as CB and SOM [280]. Purkinje cells in the cerebellum co-express two CaBPs, CB and PV [281], and data from other GABAergic types in the region encompass bipolar cells, Golgi cells, Lugaro cells, and stellate cells [282–286].

Expression information from the hippocampal formation (HF) was obtained from Hippocampome.org, a rich knowledge base of neuron types and their literature-ascribed properties, covering the dentate gyrus, CA1, CA2, CA3, the subiculum, and entorhinal cortex. In the neocortex, unique and well-known types with expression information include, among others, double bouquet cells, which are positive for CB, CR, CCK, and VIP, and Martinotti cells, which are also positive for CB, CR, and CCK in addition to famously expressing SOM and RLN [6,287–294]. Finally, striatal neurogliaform cells express NPY [295]. However, expression data for these 15 markers in medium spiny neurons is sparse; they lack 5-HT3 [296] and a subset of them may express ENK [297]. Molecular expression data of the 15 neurochemical markers were also considered for the olfactory bulb and retina, but this information is largely not localized to neuron types.

As knowledge of expression patterns becomes more complete across the molecular and anatomical dimensions, neurochemical markers can be increasingly used to efficiently locate, label, and study neuron populations across the brain. In the meantime, known expression relationships between the markers themselves can help to fill in the gaps. A yet-to-be-published study [298] has attempted to do this by using single-cell sequencing data from 19,972 genes and 126 cells in CA1 of the mouse hippocampus. They derived a hierarchical classification of CA1 interneurons and, along the way, confirmed known co-expression patterns and predicted others. However, even this ambitious effort remains preliminary and incomplete.

CONCLUSION

A vast array of neurochemical markers and corresponding expression information can be used in brain research. This systematic review of 15 widely used (though not always thoroughly understood) markers has explored their structural features and shed light on their operation in the brain. We also discussed their developmental and pathological roles, cataloged information on their use as potential medicinal targets, and summarized data for their expression across brain regions and, in rare cases of availability, well-known neuron types. Together, this information aids our understanding of the molecular-level traffic in the brain, serving as a critical guidepost along the path between obtaining massive molecular-expression datasets and using them to improve knowledge and medicine.

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LIST OF ABBREVIATIONS

5-HT3	Serotonin receptor 3
aa	Amino acids
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CaBP	Calcium-binding protein

CB	Calbindin
CB1	Cannabinoid receptor 1
CCK	Cholecystokinin
CR	Calretinin
DGI-DB	Drug-gene interaction database
ENK	Enkephalin
GABA	Gamma-aminobutyric acid
GABA_{Aα1}	Gamma-aminobutyric acid receptor A, α1 subunit
mGluR	Metabotropic glutamate receptor
mGluR1a	Metabotropic glutamate receptor 1, splice variant a
NMDA	<i>N</i> -methyl-D-aspartate
NPY	Neuropeptide Y
NT	Neurotransmitter
PV	Parvalbumin
RLN	Reelin
SOM	Somatostatin
sub P rec	Substance P receptor
vGAT	Vesicular GABA transporter
vGluT	Vesicular glutamate transporters
VIP	Vasoactive intestinal polypeptide

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Fig. (1).

Overview of molecular marker categories and functionality (examples in *italics*; markers reviewed here shown in **bold**). (1) Vesicular transporters pack and regulate concentrations of NTs in vesicles. (2) Action potential depolarizes membrane and leads to Ca²⁺ channel conformational changes. (3) Influx of Ca²⁺ through channels. (4) Ca²⁺ -binding proteins buffer and regulate calcium levels in the cell. (5) High Ca²⁺ concentration triggers vesicle-membrane fusion. (6) Vesicles open; contents dumped into synaptic cleft. (7) NTs and peptides reversibly bind to receptors on dendrite. (8) Extracellular matrix proteins modulate plasticity and regulate neuronal development, among other functions. (9) Transporters move recycled or newly synthesized NTs into cell.

Fig. (2).

In addition to prominent roles in central and peripheral nervous systems, most of the neurochemical markers reviewed also play roles outside nervous tissue. Here, we summarize their expression in five other body systems (see Table 2 and text for details). Note that 7/15 markers play roles in both digestion and the endocrine system.

Fig. (3).

A – Across twelve high-level brain regions, in situ hybridization expression levels were extracted from the Allen Brain Atlas for the 15 gene precursors of the markers reported here (markers in parentheses). Log₂ values of expression energies are shown. **B** – At the neuron type level, marker expression information is much sparser and is restricted to certain neuron types in specific sub-regions. Known molecular marker expression (black squares) or lack thereof (white) for 42 major neuron types across brain regions; unknown information indicated by gray squares with X's. Abbreviations for panel B: HF – hippocampal formation, DG – dentate gyrus.

Table 1

Nomenclature and structural features for 15 major molecular markers across five categories in mice.

Category	Marker (UniProt accession number)	Synonyms, related names, and abbreviations	Subcellular localization(s)	Sequence length (aa)	Molecular weight (kDa)	Isoelectric point (pI)	Hydropathy (GRAVY)
Transporters	vGluT3 (Q8BFU8)	Solute carrier family 17 (sodium phosphate), member 3; Solute carrier family 17 (vesicular glutamate transporter), member 3	Cytoplasmic vesicle membrane	601	66.148	6.05	0.186
	CB (P12658)	Brain-2; CaBP; Calb; Calb-I; Calb1; Calbindin 1 (28kD); Calbindin D28 k; Calbindin D28K; Calbindin-28K; Calbindin-D28K; PCD-29; Spot 35 protein; Vitamin D-dependent calcium-binding protein, avian-type	Cytosol, nucleus, axon, dendrite, synapse	261	29.996	4.71	-0.484
Ca ²⁺ proteins binding	CR (Q08331)	CAL2; Calb2; Calbindin 2; Calbindin 2 (29kD)	Cytosol, nucleus, terminal bouton, synapse	271	31.374	4.94	-0.655
	PV (P32848)	parvalbumin alpha	Cytosol, nucleus, axon, terminal bouton	110	11.931	5.02	-0.355
	CCK (P09240)	--	Nucleus, axon, axon hillock, axon initial segment, dendrite, extracellular matrix	115	12.770	9.44	-0.381
	ENK (P22005)	ENK; Penk; Penk1; PPA; preproenkephalin 1; Proenkephalin; Proenkephalin-A	Nucleus, axon, dendrite, plasma membrane, extracellular matrix	268	31.004	5.55	-0.821
Neuropeptides	NPY (P57774)	C-flanking peptide of NPY; CPON; Neuropeptide tyrosine; Neuropeptide Y; NPY	Nucleus, axon, cytosol, extracellular matrix	97	10.874	6.56	-0.405
	SOM (P60041)	Antrin; preprosomatostatin;	Nucleus, extracellular matrix	116	12.746	5.47	-0.290

Category	Marker (UniProt accession number)	Synonyms, related names, and abbreviations	Subcellular localization(s)	Sequence length (aa)	Molecular weight (kDa)	Isoelectric point (pH)	Hydropathy (GRAVY)
Receptors		SMS; Smst; SOM; Somatostatin; Somatostatin-14; Somatostatin-28; SRIF; SS; Sst					
	VIP (P32648)	Intestinal peptide PHI-27; Intestinal peptide PHI-42; MGC107202; Peptide histidine isoleucinamide 27; PHI, peptide histidine isoleucine; Vasoactive intestinal peptide; Vasoactive intestinal polypeptide; VIP; VIP peptides	Nucleus, extracellular matrix	170	19.049	6.13	-0.416
	mGluR1a (P97772)	Isoform 1, a, or alpha of the following: G protein-coupled receptor, family C, group 1, member A; Glutamate receptor, metabotropic 1; Glutamate receptor, metabotropic, type I; Gpr1a; Grm1; GRM1A; mGlu1 receptor; mGluR1	Post-synaptic cell membrane	1,199	133.212	6.44	-0.122
	GABA _A α1 (P62812)	GABA A receptor alpha 1 subunit; GABA(A) receptor alpha (1); GABA(A) receptor alpha 1; GABA(A) receptor subunit alpha(1); GABA(A)Ralpha(1) subunit; GABA-A receptor subtype alpha 1; GABAA receptor alpha1 subunit; GABAA receptor subunit alpha 1; Gabra-1; Gabra1; gamma-Aminobutyric acid (GABA) A receptor	Post-synaptic cell membrane	455	51.754	9.34	-0.234

Category	Marker (UniProt accession number)	Synonyms, related names, and abbreviations	Subcellular localization(s)	Sequence length (aa)	Molecular weight (kDa)	Isoelectric point (pH)	Hydropathy (GRAVY)
		alpha 1 subunit; gamma-Aminobutyric acid type A receptor alpha-1 subunit (GABRA1)					
	5-HT3 (P23979)	5-HT ₃ ; 5-HT ₃ ; 5-HT ₃ receptor; 5-HT _{3A} ; 5-HT _{3A} ; 5-HT _{3R} ; 5-hydroxytryptamine (serotonin) receptor 3A; 5-hydroxytryptamine receptor 3; 5-hydroxytryptamine receptor 3A; 5ht ₃ ; 5HT ₃ serotonin receptor; 5HT _{3A} ; Htr3; Htr3a; Serotonin receptor 3A; Serotonin-gated ion channel receptor	Post-synaptic cell membrane	487	56.056	6.15	0.091
	CB1 (P47746)	Brain-type cannabinoid receptor; Cannabinoid receptor 1 (brain); Cannabinoid receptor CB1; CB-R; CB1 receptor; CB1R; CNR; CNR1; Cnr1	Pre- and post-synaptic cell membrane	473	52.831	8.58	0.333
	sub P rec (P30548)	Neurokinin-1 receptor; NK-1 receptor; NK1 (substance P) receptor; NK1-R; NK1R; SPR; Tachykinin NK1 receptor; Tacr1	Pre- and post-synaptic cell membrane	407	46.322	7.56	0.322
Matrix proteins	RLN (Q60841)	CR-50 antigen; extracellular matrix serine protease; reeler; Reeler protein; Rln; Rl	Extracellular matrix, dendrite, cytosol	3,461	387.495	5.44	-0.264

Table 2

Key roles for the selected molecular markers (continues next page).

Category	Marker	Neurological role(s)	Other functional role(s)	Developmental role(s)	Pathological role(s)
Transporters	vGluT3	<ol style="list-style-type: none"> 1 Transport and packing of glutamate into vesicles; may be co-released with GABA or serotonin 2 Buffer of cytoplasmic glutamate 	Unknown, mRNA expressed in liver and kidney	Released transiently in selected cells; role unclear	Nonsyndromic hearing impairment
		<ol style="list-style-type: none"> 1 Co-localizes and interacts with plasma membrane Ca^{2+} pump 2 Binds calcium ions to buffer and regulate cytosolic levels 3 Helps govern action potential duration 4 Neuroprotective agent during periods of high activity 	<ol style="list-style-type: none"> 1 Transcellular Ca^{2+} movement in kidney distal tubules and intestinal absorptive cells 2 Controls insulin release in islet cells of the pancreas 3 Modulates apoptosis, reportedly by binding caspase-3 and altering its activity, in osteoblasts that mineralize bone 	Regulates Ca^{2+} pools critical for synaptic plasticity	<ol style="list-style-type: none"> 1 Reduced CB expression aggravates Alzheimer's disease 2 In Huntington's disease, reduction in CB+ neurons may contribute to apoptosis 3 Loss of CB+ neurons may lead to degeneration of the substantia nigra
Ca^{2+} -binding proteins	CR	<ol style="list-style-type: none"> 1 (See CB) 2 Expressed in retina and somatosensory pathways (e.g. cochlear nuclei and olfactory bulb) 3 Also induces LTP 	<ol style="list-style-type: none"> 1 Expressed in lung mesothelium 2 Detected in Leydig cells of the testis, theca lutein and theca interna cells of the ovary 3 Weak-moderate expression found in sustentacular and cortical cells of adrenal gland 4 Expressed in mast cells and mast cell lesions of the skin 	(See CB)	<ol style="list-style-type: none"> 1 CR absent from nerves in the bowel in Hirschsprung disease 2 In mesothelioma, CR differentially expressed in malignant and benign lung tumors 3 Decreased CR expression in hippocampus linked with temporal lobe epilepsy
	PV	(See CB)	Involved in muscle relaxation after contraction (shuttles Ca^{2+} from cytosol to intracellular stores to accelerate relaxation of fast-twitch fibers)	(See CB)	Decreased PV expression in schizophrenia; disruption may affect synchronization of cortical circuits

Category	Marker	Neurological role(s)	Other functional role(s)	Developmental role(s)	Pathological role(s)
Neuropeptides	CCK	<ol style="list-style-type: none"> 1 Modulates the effects of glutamate, GABA, dopamine, and serotonin 2 Increased CCK activity on exposure to stress, suggesting it might participate in stress response 3 Role in memory 	<ol style="list-style-type: none"> 1 Induces gall bladder contraction and the release of pancreatic enzymes in the gut 2 Hunger suppressant 	Unclear, but CCK is detected in the nervous system as early as embryonic day 8 (E8) and in the digestive system by E15	<ol style="list-style-type: none"> 1 Cause of visual hallucinations in Parkinson's disease 2 Colorectal carcinomas produce CCK
	ENK	<ol style="list-style-type: none"> 1 Pain perception and analgesia 2 Respond to stress 3 Present in peripheral nerves of the digestive system, but role unclear 	Detected within immune cells in inflamed subcutaneous tissue	Help to regulate cell proliferation	<ol style="list-style-type: none"> 1 Role in addiction and reward systems 2 Shown to induce seizures
	NPY	<ol style="list-style-type: none"> 1 Regulates food intake and storage of energy as fat 2 Presence in peripheral system linked to vasoconstriction in cardiac tissue 		During development, NPY expression corresponds to levels of maternal food provision [241]	<ol style="list-style-type: none"> 1 Increases in NPY mRNA and NPY release linked to obesity, anorexia, and bulimia 2 Related to alcoholism
	SOM	<ol style="list-style-type: none"> 1 Memory formation and shaping of neuronal activity and plasticity 2 Pain perception 	<ol style="list-style-type: none"> 1 Anterior pituitary: inhibits release of growth hormone, thyroid-stimulating hormone, prolactin 2 In the stomach, reduces production and secretion of gastric acid 	Influences synaptogenesis, proliferation of cerebellar neuroblasts, and axonal pathfinding [242,243]	<ol style="list-style-type: none"> 1 Associated with epilepsy 2 Alterations reported in neurodegenerative diseases including Alzheimer's, Parkinson's, and multiple sclerosis
	VIP	<ol style="list-style-type: none"> 1 Local energy metabolism and usage via glycogenolysis 2 Neuroprotection 3 Circadian rhythm regulation: synchronizes timing of suprachiasmatic nuclei function with the environmental light-dark cycle 	Digestive: relaxation of smooth muscles to increase motility; inhibition of absorption and stimulation of water and electrolyte secretion	<ol style="list-style-type: none"> 1 Development of neural tube 2 Role in neurogenesis 	<ol style="list-style-type: none"> 1 Linked to neurodevelopmental disorders, including autism, Down syndrome, and fetal alcohol syndrome 2 Associated with temporal-lobe epilepsy

Category	Marker	Neurological role(s)	Other functional role(s)	Developmental role(s)	Pathological role(s)
Receptors		<p>4 Expressed in peripheral nerves, including cardiovascular (vasodilation; enhanced myocardial contractility), respiratory (pulmonary vasodilation), kidney (diuresis; increased excretion of Na⁺ into urine; stimulation of renin release), and reproduction (increased blood flow to reproductive organs)</p>			
	mGluR1a	<p>1 Binds glutamate and initiates a host of electrical and chemical signaling pathways</p> <p>2 Regulates ion channels and cell excitability</p> <p>3 Auto-regulates synaptic transmission by reducing pre-synaptic release of glutamate</p> <p>4 Implicated in LTP and LTD</p> <p>5 Peripheral nerves: in the rat heart, localized in atrial nerve terminals, ganglion cells, and elements of conducting system</p>	<p>1 Cardiovascular: affect cardiac atrial cells</p> <p>2 Immune: expressed in thymus</p> <p>3 Skeletal: detected in osteocytes and found to play a role in bone resorption</p> <p>4 Endocrine: expressed in adrenal gland; may play a role in stress response</p> <p>5 Expressed in retina, inner ear, and involved in pain perception</p>	Minimal role during embryonic and prenatal development	<p>1 Linked to Huntington's disease and multiple sclerosis</p> <p>2 Ulcer formation</p> <p>3 Melanoma</p>
	GABA _{Aα1}	<p>1 Binds GABA and initiates a post-synaptic inhibitory electrical response</p> <p>2 Differential usage in synapses between hippocampal CA1 basket cells and post-synaptic pyramidal cells. Utilized by PV⁺ basket cells; not by CCK⁺</p>	Identified in adrenal gland, gonads, and small intestine	Minimal role during embryonic and prenatal development	Links to several neurological and psychiatric diseases, including epilepsy, Huntington's disease, anxiety disorders, alcoholism, and schizophrenia

Category	Marker	Neurological role(s)	Other functional role(s)	Developmental role(s)	Pathological role(s)
	5-HT3	<ol style="list-style-type: none"> 1 Binds the neurotransmitter serotonin 2 Mediates fast excitatory transmission in rat neocortical interneurons, amygdala, and hippocampus, and in ferret visual cortex. 3 In hippocampus (CA1), receptor antagonists cause induction of LTP and improvement in recall and spatial memory 4 Modulation of dopamine release, both through agonist and antagonist activity 5 Peripheral nervous mediation of signals of nausea, pain, and bloating in the gut 		Serotonin present, but receptor roles not well documented [244]	Modulation on the effects of abused drugs, including cocaine, amphetamines, nicotine, and morphine
	CB1	<ol style="list-style-type: none"> 1 Binds endo-, plant, and synthetic cannabinoids 2 Pre-synaptic inhibition of NT release 3 Mediates depolarization-induced suppression of inhibition, a form of short-term GABAergic plasticity 	<ol style="list-style-type: none"> 1 Immune: detected in spleen and white blood cells; mediate cannabinoid-induced immunosuppression 2 Expression also detected in heart and gonads 	Present as early as E11 [245]	<ol style="list-style-type: none"> 1 Prominent role in drug abuse 2 Increased binding detected in schizophrenia and Parkinson's disease
	sub P rec	<ol style="list-style-type: none"> 1 Binds substance P 2 Modulates pain perception, inflammatory response, and adaptive stress response 	<ol style="list-style-type: none"> 1 Digestive: regulation of muscle activity in intestine, vasodilation, mediation in inflammation processes 2 Endocrine: binding of substance P to receptors reduces duration of response to stress 	High of substance P expression before birth decreases to adult levels by P14.	<ol style="list-style-type: none"> 1 Linked to chronic pain 2 Role in development of obesity

Category	Marker	Neurological role(s)	Other functional role(s)	Developmental role(s)	Pathological role(s)
Matrix proteins	RLN	1 Participates in adult neurogenesis	1 Involved in development and cellular migration of small intestine	1 Regulates processes of neuronal migration and positioning	1 Dysregulation of Reln gene linked with various cancers
		2 Modulates synaptic plasticity by enhancing the induction and maintenance of LTP 3. Stimulates dendrite and dendritic spine development and regulates the continuing migration of neuroblasts generated in subventricular and subgranular zones	2 Linked to bone and tooth formation	2 Plays a role in layering of neurons in the cortex, hippocampus, and cerebellum	2 Reduced expression detected in schizophrenia and bipolar disorder
			3 Also expressed in liver, blood (plasma and cells), and reproductive organs		3 Also implicated in autism and Alzheimer's disease

Table 3

Selected drugs that target molecular marker receptors.

Marker	Gene for receptor	DGI-DB hits (score 5)	Sampling of drugs	Drug indication	Interaction type	Reference
CCK	<i>CKKAR</i>	6 (1)	Dexlorgluidide	In clinical trials in Europe for the treatment of Irritable Bowel Syndrome and Gastroesophageal Reflux Disease; US trials discontinued	Antagonist	[252]
	<i>CCKBR</i>	12 (1)	Pentagastrin	Diagnostic aid for evaluation of gastric acid secretory function	Agonist	[253]
ENK	<i>OPRD1</i>	53 (16)	Butorphanol	Moderate to severe pain	Agonist	[254]
			Morphine	Relief and treatment of severe pain	Agonist	[255]
			Naloxone	Reversal of narcotic depression induced by opioids and opioid overdose; to increase blood pressure in management of septic shock	Antagonist	[256]
	<i>OPRM1</i>	84 (32)	Fentanyl	Treatment of cancer patients with severe pain	Agonist	[257]
NPY			Methadone	Pain; drug withdrawal syndrome; opioid type drug dependence; dry cough	Agonist	[258]
			Sufentanil	General anesthesia	Agonist	[259]
	<i>NPY1R</i>	2 (0)	--			
	<i>NPY2R</i>	2 (0)	--			
	<i>NPY4R</i>	0	--			
	<i>NPY5R</i>	4 (1)	Velneperit	Obesity	Antagonist	[260]
SOM	<i>NPY6R</i>	0	--			
	<i>SSTR1</i>	10 (2)	Octreotide	Acromegaly; side effects from cancer chemotherapy	Binder	[261]
			Pasireotide	Cushing's syndrome	Binder	[262]
	<i>SSTR2</i>	13 (2)	[Octreotide & Pasireotide]	[see above]	[see above]	[261,262]
	<i>SSTR3</i>	15 (1)	[Pasireotide]	[see above]	[see above]	[262]
	<i>SSTR4</i>	7 (0)	--			
VIP	<i>SSTR5</i>	15 (2)	[Octreotide & Pasireotide]	[see above]	[see above]	[261,262]
	<i>VIPR1</i>	2 (0)	--			
	<i>VIPR2</i>	2 (0)	--			
mGluR1a	<i>GRM1</i>	10 (0)	--			
GABA _{Aα1}	<i>GABRA1</i>	84 (41)	Pentobarbital	Short-term treatment of insomnia	Potentiator	[263]
			Thiamylal	General anesthesia; inducing a hypnotic state	Agonist	[264]

Marker	Gene for receptor	DGI-DB hits (score 5)	Sampling of drugs	Drug indication	Interaction type	Reference
5-HT3	<i>HTR3A</i>	54 (8)	Phenobarbital	Seizures	Potentiator	[265]
			Ethanol	Chronic pain in such conditions as inoperable cancer and trigeminal neuralgia	Agonist	[266]
			Ondansetron	Alcohol use disorders; chemotherapy-induced nausea and vomiting	Agonist	[267,268]
			Granisetron	Nausea and vomiting	Antagonist	[269]
			--			
	<i>HTR3B</i>	5 (0)	--			
	<i>HTR3C</i>	4 (0)	--			
	<i>HTR3D</i>	4 (0)	--			
	<i>HTR3E</i>	4 (0)	--			
	<i>CNR1</i>	10 (3)	Dronabinol	Anorexia; chemotherapy-induced nausea and vomiting; disturbed behavior in Alzheimer's	Agonist	[270]
CB1	<i>TACR1</i>	30 (1)	Nabilone	Chemotherapy-induced nausea and vomiting	Partial agonist	[271]
			Rimonabant	Obesity	Antagonist	[272]
			Aprepitant	Chemotherapy-induced nausea and vomiting	Antagonist	--