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Review

Protein complexes as psychiatric and neurological drug targets

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ABSTRACT

The need for improved medications for psychiatric and neurological disorders is clear. Difficulties in finding such drugs demands that all strategic means be utilized for their invention. The discovery of forebrain specific AMPA receptor antagonists, which selectively block the specific combinations of principal and auxiliary subunits present in forebrain regions but spare targets in the cerebellum, was recently disclosed. This discovery raised the possibility that other auxiliary protein systems could be utilized to help identify new medicines. Discussion of the TARP-dependent AMPA receptor antagonists has been presented elsewhere. Here we review the diversity of protein complexes of neurotransmitter receptors in the nervous system to highlight the broad range of protein/protein drug targets. We briefly outline the structural basis of protein complexes as drug targets for G-protein-coupled receptors, voltage-gated ion channels, and ligand-gated ion channels. This review highlights heterodimers, subunit-specific receptor constructions, multiple signaling pathways, and auxiliary proteins with an emphasis on the later. We conclude that the use of auxiliary proteins in chemical compound screening could enhance the detection of specific, targeted drug searches and lead to novel and improved medicines for psychiatric and neurological disorders.

1. Medicines for psychiatric and neurological disorders

Prevention of disease and the arrest or mitigation of disease symptoms relies heavily on the availability of medicines. For many diseases, the drug choices for physicians vary widely. For other diseases, there are limitations. For example, in obsessive-compulsive disorder, the pharmacological arsenal is restricted primarily to the selective serotonin uptake inhibitors (SSRIs) where doses higher than used in major depressive disorder are typically given for long periods without high probability of significant symptom relief [1]. Likewise, in the management of agitation in neurodegenerative diseases, there are few pharmacological treatment options [2]. In other cases, the restriction of available medicines is due to the special group of patients that responds to treatment but continues to suffer with unresponsive symptoms [3]. Another group of patients, designated as treatment resistant, do not respond to any of the large variety of medications available. The latter case is well illustrated by depressed patients that do not respond to SSRIs, to SSRI plus adjunct medication, or to electroconvulsive therapy [4]. At a time when many had argued that medical investigators had reached the limit of their understanding of how to help these patients,

Abbreviations: AM, adrenomedulin; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMY, amylin; AT, angiotensin type; β-CCT, beta-carboline-3-carboxylate-t-butyl ester; CT, calcitonin; CTR, calcitonin receptor; CLR, calcitonin receptor-like receptor; DZ, diazepam; GIRK, G-protein-activated inwardly rectifying potassium channel; GPCR, G-protein-coupled receptor; HCN, hyperpolarization-activated cyclic nucleotide-gated; K_{ATP}, ATP-sensitive potassium channel; KCO, potassium channel opener; KCTD, potassium channel tetramerization domain; Kir, inward rectifying potassium channels; KRM-II-81, 5-(8-ethynyl-6-(pyridin-2-yl)-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepin-3-yl)oxazole; L-655,708, ethyl (S)-11,12,13,13a-tetrahydro-7-methoxy-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate; L-838,417, 7-(tert-Butyl)-3-(2,5-difluorophenyl)-6-((1-methyl-1H-1,2,4-triazol-5-yl)methoxy)-[1,2,4]triazolo[4,3-b]pyridazine; LGIC, ligand-gated ion channel; LY3130481 = CERC-611, 6-[(1S)-1-[1-[5-(2-hydroxyethoxy)-2-pyridyl]pyrazol-3-yl]ethyl]-3H-1,3-benzothiazol-2-one; MiRP1, mink-related protein 1; MOR, μ-opioid receptor; MRK-409 (MRK-0343), 7-Cyclobutyl-3-(2,6-difluorophenyl)-6-[(1-methyl-1H-1,2,4-triazol-5-yl) methoxy]-1,2,4-triazolo[4,3-b]pyridazine; PF-05089771, 4-[2-(5-Amino-1H-pyrazol-4-yl)-4-chlorophenoxy]-5-chloro-2-fluoro-N-1,3-thiazol-4-ylbenzenesulfonamide; PIP2, phosphatidylinositol 4,5-bisphosphate; PTH, parathyroid hormone; PWZ-029, 8-chloro-3-(methoxymethyl)-5-methyl-4H-imidazo[1,5-a][1,4]benzodiazepin-6-one; PZ-II-029, 7-methoxy-2-(4-methoxyphenyl)-2*H*-pyrazolo[4,3-*c*]quinolin-3(5*H*)-one; RAMP, receptor activity-modifying protein; RY-080, ethyl 8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate; SGS-742 (CGP-36742, DVD-742), (3-Aminopropyl)butylphosphinic acid; TP-003, 2′,4-Difluoro-5′-[8-fluoro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-*a*]-pyridin-3-yl]-[1,1′-biphenyl]-2-carbonitrile; TPA-023, 7-(1,1-dimethylethyl)-6-(2-ethyl-2H-1,2,4-triazol-3-ylmethoxy)-3-(2-fluorophenyl)-1,2,4-triazolo[4,3-b]pyridazine; TRV027, (2R)-2-[[(2S)-1-[(2S)-2-[[(2S,3S)-2-[[(2S)-2-[[(2S)-2-[[(2S)-5-(diaminomethylideneamino)-2-[[2-(methylamino)acetyl]amino]pentanoyl]amino]-3-methylbutanoyl]amino]-3-(4-hydroxyphenyl)propanoyl]amino]-3-methylpentanoyl]amino]-3-(1H-imidazol-5-yl)propanoyl]pyrrolidine-2-carbonyl]amino]propanoic acid; SUR, sulfonylurea protein; TRV130, oliceridine; VGCC, voltage-gated calcium channel; VGIC, voltage-gated-ion channel; Xli-093, bis[8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid] 1,3-propanediyl ester hydrate; ZD 7288, 4-ethylphenylamino-1,2-dimethyl-6-methylaminopyrimidinium chloride

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clinical findings with ketamine, a drug first synthesized in 1962, [5,6] brought renewed hope and remarkably energized efforts to discover improved treatment options [7]. It is important to recognize here one avenue for speeding medicines to patients: experimental clinical investigation [8,9]. Trullas and Skolnick [10] made preclinical predictions that ketamine would be effective in depression 10 years prior to the clinical investigations. Ten years.

Medicines are discovered in two major ways. First, via data on human disease and biology. When it was observed by natural experiment that birch bark fungus had antibiotic properties, and efficacy against intestinal parasites such as whipworm, it ultimately became the medicine carried on the mountain adventures of the 5300 year old man, Otzi [11]. When it is observed that rodents appeared calmer with the phenothiazine promethazine, it was suggested that it might be used as a pre-anesthetic in patients. The observed calming effect in these patients directly led to further clinical study that led to the use of the newer molecule chlorpromazine (Thorazine), only one year after its synthesis. This rapid transition of observation to clinical trial enabled the psychopharmacological revolution in the early 1950s (c.f. Witkin [7]). Human data continues to be a predominant source of the richest information guiding drug discovery. This type of drug discovery approach is based on observations of biological effect and/or functional outcome (phenotype) (phenotypic drug discovery [PDD]), and enable interrogation of relevant signaling pathways and molecular targets in an agnostic and empirical manner. Phenotypic screening has had a long history and continues to pose a powerful and vital strategy with evolving sophistication in the assessment of phenotypes [12]. More first-in-class small-molecule drugs approved by FDA between 1999 and 2008 were identified by functional phenotypic lead generation strategies than contemporary molecular targeted strategies [13].

A second major avenue for the discovery of new medicines comes from hypothesis-driven, mechanism-based drug design. Drug discovery directed toward specific molecular targets is currently the most common approach known as targeted drug discovery (TDD). TDD approaches test hypotheses concerning specific gene/protein targets utilizing a plethora of methods and new technologies including automation, structural biology, and advanced chemistry technologies [14]. PDD and TDD are complementary strategies. Both strategies ultimately make use of currently available knowledge of the physiology and pathophysiology of disease and available technology and datasets. Computer-aided prediction of pharmacophore structures based on the ternary structure of drug target proteins is one very powerful example [15,16]. Rapid development of next-generation sequencing (NGS) technologies and genome-wide-association (GWAS) studies are making genome-tailored medicine easier [17]. Grafts of patient-derived induced pluripotent stem cells (iPS cells) provides unprecedented treatment strategies in numbers of diseases [18], including age-related macular degeneration currently under first-in-human trials [19]. The new technologies of CRISPR-Cas nucleases and TALENs paved the way for gene editing to enter clinical practice [20,21].

Neurological and psychiatric drugs modulate pathological neuronal activity, neurotransmitter release, and tone and thereby mitigate disease symptoms as exemplified by the lidocaine family of drugs as local anesthetics, 1,4-benzodiazepines as antiepileptics [22], anxiolytics [23], sleep-inducing drugs [24] and selective serotonin/norepinephrine reuptake inhibitors for treatment of depression, anxiety [25] and chronic pain [26]. The emergence of optogenetics and chemogenetics added powerful tools to manipulate the activity of specific neural circuits where the light-operated ion channels or chemical-operated GPCRs are expressed [27,28]. A human clinical trial has recently begun to examine whether the light-operated ion channel, channelrhodopsin-2, can be used to restore light sensitivity in the degenerative eye disease retinitis pigmentosa [29]. Even as various gene-therapy technologies emerge, pharmacological strategies will be vital and likely to continue to be common in the future. Ultimately, however, compounds must be constructed to interact in specific ways with a biological target (e.g., a protein). With all the biological understanding we can muster, medicinal chemists and their biological partners must properly connect the chemical to its target. This stage of the discovery process can be markedly hampered or brought to a standstill by technical demands that cannot at the time be surmounted.

The sodium channel, Nav1.7, for example has long been hypothesized to control pain since mutations in the gene in humans induces loss of pain sensitivity [30,31]. This human-validated analgesic target is understandably of great interest for the development of new pain therapies. The close structural homology across Nav family proteins, however, has made it difficult to generate Nav1.7-selectivity. Currently, the majority of therapeutically used Nav channel blockers bind to highly conserved residues that are found within the pore domain of the channel, making selectivity between family members difficult to achieve [32]. One way of improving selectivity is to design compounds that bind to areas outside of the conserved pore-forming region. PF-05089771 (Pfizer) is one such compound, with 1000-fold selectivity for Nav1.7 over Nav1.5 and Nav1.8, and is currently in clinical trials for use in chronic pain. The compound has been reported to be well tolerated in phase I trials [33].

2. Protein complexes as drug targets

Multiple biological and chemical approaches can be invoked to help solve the problem of finding molecules that selectively interact with drug receptors. We have argued elsewhere that the use of auxiliary proteins might enhance the discovery process [34,35]. Many of the most common neurological disorders, such as epilepsy and pain, involve abnormalities of neuronal excitability. However there are multiple difficulties and issues involved in the use of technologies such as invasive surgery for gene delivery and immunogenicity by exogenous gene expression [29,36]. The region/circuit specific regulation of neural activities by pharmacological agents targeting endogenously expressed proteins at present is more practical for patients. AMPA-type ionotropic glutamate receptors play the major role in excitatory synaptic transmission. AMPA receptors are associated with multiple auxiliary subunits [34,37]. The AMPA receptor auxiliary subunits, TARPs (Transmembrane AMPA receptor regulatory proteins) dramatically modulate AMPA receptor functions, including cell surface trafficking, synaptic targeting, gating and pharmacology [37]. In addition, members of the TARP family are differentially expressed in specific brain regions [38,39]. The two prominent properties of TARPs, pharmacological modulation of AMPA receptors and brain region-specific expression inspired us to develop brain region-selective AMPA receptor modulators exemplified by the first AMPA receptor antagonist, LY3130481 (CERC-611). This molecule was rationally designed to dampen excitatory neurotransmission in forebrain by not hindbrain [34,40] and for which another series of compounds was also reported [41]. These selective antagonists retained the anticonvulsant efficacy of non-selective AMPA receptor antagonists but avoided the ataxia engendered by non-selective drugs like the antiepileptic agent perampanel [40]. The design approach for these molecules utilized a chemical screen for molecules in functional assays in cells detecting activity at GluA1 + the auxiliary protein TARP γ-8 (primarily forebrain) vs. GluA1 + TARP γ-2 (primarily cerebellar).

Given the success of this approach (rational discovery) [34,35] in generating a novel molecule (CERC-611) currently undergoing clinical development for epilepsy and the medical value of other such drugs that target auxiliary proteins (serendipitous discovery as in gabapentin), the present review will highlight a number of other drug targets that have auxiliary proteins or accessory protein subunit assemblies. The aim of this overview is to suggest new potential drug targets with the aim of finding improved pharmacological approaches to enhance the efficacy and reduce the side-effect burden of new medicines. In this review, we will briefly outline the structural basis for protein complexes as drug targets for G-protein-coupled receptors, voltage-