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Neural Modulation Strategies in Neuroscience

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Abstract

Chemogenetics is a powerful and versatile neuromodulation strategy that enables remote, reversible control of defined cell populations through the use of engineered receptors and pharmacologically inert small-molecule ligands. This review synthesizes the current state of chemogenetic technologies, focusing on Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) and emerging ion-channel-based actuators, and outlines their molecular mechanisms, ligand pharmacology, and recent technical innovations. We examine the broad applications of these tools in disease modeling, behavioral neuroscience, and experimental therapeutics, as well as in biomedical contexts beyond the central nervous system. Particular attention is given to the role of chemogenetics in mapping and causally dissecting neural circuits, where it provides precise and reversible modulation of neuronal activity to elucidate the cellular substrates of behavior.

Comparisons with other neuromodulation techniques—such as optogenetics and electrical stimulation—are discussed, together with practical considerations including ligand selection, delivery strategies, and long-term applications. Finally, we highlight the translational trajectory of chemogenetic technologies, emphasizing ongoing advances that are bringing gene therapy-based neuromodulation closer to clinical application in neurology and psychiatry.

Keywords: Chemogenetics, DREADD, neuromodulation, neural circuits, behavioral neuroscience, gene therapy

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INTRODUCTION

Chemogenetics is an advanced neuromodulation strategy that is often described as a molecular "switch." In this method, cells are engineered to express artificial receptors that can be selectively activated by a chemical compound that, under normal physiological conditions, has no biological effect. This design effectively reverses the conventional pharmacological paradigm: instead of designing drugs that target naturally occurring receptors, chemogenetics constructs receptors that selectively respond to a chosen synthetic molecule. The conceptual roots of chemogenetic research date back to the early 1990s, when Strader and colleagues showed that G protein-coupled receptors (GPCRs) could be engineered to recognize non-natural ligands rather than their endogenous neurotransmitters (1,2). These initial studies demonstrated that receptor-ligand specificity could be rationally redesigned, paving the way for today's chemogenetic platforms. Modern adaptations of this idea, most notably the DREADD (Designer Receptors Exclusively Activated by Designer Drugs) system, now provide neuroscientists with a powerful approach for selectively controlling the activity of defined neural populations (3).

FROM RASSLS TO DREADDS: CHEMOGENETIC RECEPTOR DESIGN

One of the main goals of chemogenetics in neuroscience is to reach a level of anatomical and cellular precision that traditional pharmacological tools could not easily offer. By restricting the expression of designer receptors to selected neuronal subtypes, researchers can either silence or activate specific circuits without affecting other brain regions. Unlike systemic drug treatments, which broadly act on all cells carrying the natural receptor, chemogenetic modulation is confined to the targeted population. Furthermore, it is reversible and noninvasive: the receptors are typically delivered through viral vectors or transgenic approaches, and neural activity is modulated simply by administering the activating compound, avoiding the need for implants or tissue lesions. These advantages have made chemogenetics a key technique for mapping causal relationships between neural circuits and behavior (4). Over the past decade, it has been widely adopted to dissect neural circuitry underlying behaviors, perceptions, and pathologies in species ranging from fruit flies to non-human primates (5,6). By enabling researchers to turn specific neural circuits "on" or "off" like a switch, chemogenetics bridges the gap between correlational observations and causal interrogation of brain function.

At the heart of these methods are engineered receptor-ligand pairs. The DREADD family of modified GPCRs remains the most widely applied. These receptors are designed to lose responsiveness to endogenous neurotransmitters but can be activated by an otherwise inert drug, usually clozapine-N-oxide (CNO) (7). Importantly, DREADDs remain functionally silent in the absence of the ligand, minimizing interference with normal cellular physiology. This represented a major improvement over the earlier generation of receptors, known as RASSLs (Receptors Activated Solely by Synthetic Ligands), which showed spontaneous activity even in the absence of ligand binding (8). With DREADDs, neuronal activity can thus be precisely toggled only when and where the experimenter delivers the activating molecule.

Subsequent receptor engineering expanded the chemogenetic toolkit. A notable advance was the κ-opioid-derived DREADD, termed KORD, which is selectively activated by salvinorin B, an inactive metabolite of the hallucinogen salvinorin A. The KORD couples to inhibitory G proteins (Gi) and can be co-expressed with an excitatory DREADD in the same neurons, permitting bidirectional modulation with two different drugs (9).

ION CHANNEL-BASED CHEMOGENETIC ACTUATORS: THE PSAM/PSEM SYSTEM

Beyond GPCRs, chemogenetic systems based on ion channels have been developed to directly alter membrane excitability. One prominent example is the PSAM/PSEM system (Pharmacologically Selective Actuator Module / Pharmacologically Selective Effector Molecule) introduced by the Sternson group (10). The PSAMs are chimeric ligand-gated ion channels. They combine a modified ligand-binding domain, such as one derived from the α7 nicotinic acetylcholine receptor, with the ion-conducting domain of another receptor, such as the 5-HT3 or glycine receptor. Their synthetic ligand (PSEM) selectively opens the engineered channel (10). Depending on the channel used, PSAMs can depolarize or hyperpolarize neurons, offering either excitation or inhibition with high specificity.

Because they act through direct ion flow rather than second-messenger signaling, their effects can develop more rapidly than those of GPCR-based DREADDs. Moreover, recent PSAM variants activated by ultrapotent ligands (analogues of varenicline, a clinically used nicotinic partial agonist) have shown effective modulation of neural activity in rodents and primates. The use of a drug like varenicline (which has good brain penetration and an established safety profile in humans) as the actuator molecule highlights the translational appeal

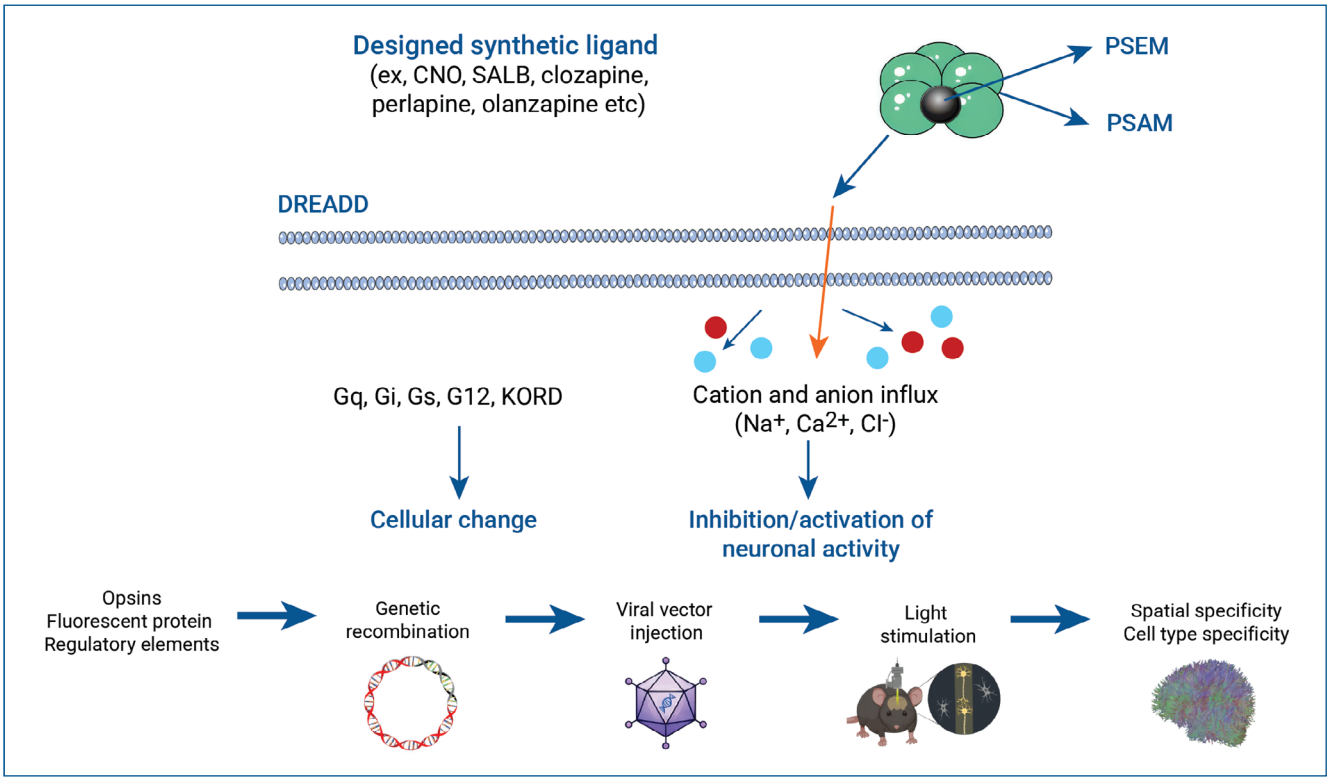

FIGURE 1. Molecular mechanisms and applications of chemogenetic neuromodulation compared with optogenetics. Chemogenetics acts as a molecular "switch" in which engineered receptors are selectively activated by otherwise inert synthetic ligands, reversing the conventional logic of pharmacology. Two principal platforms are shown. The designer receptors exclusively activated by designer drugs (DREADD) system is built on modified G protein-coupled receptors that no longer respond to endogenous neurotransmitters but are activated by designer ligands such as clozapine-N-oxide (CNO), salvinorin B (SALB, the actuator for the κ-opioid-derived KORD), clozapine, perlapine, or olanzapine. Depending on the coupled G protein (Gq, Gi, Gs, G12, or KORD), ligand binding engages second-messenger cascades that drive relatively slow but sustained cellular and metabolic changes. In parallel, the ion-channel-based pharmacologically selective actuator module / pharmacologically selective effector molecule (PSAM/PSEM) system uses chimeric ligand-gated channels: binding of the synthetic PSEM ligand opens the engineered channel and permits direct cation and anion flux (Na^+, Ca^{2+}, Cl^-), producing rapid excitation or inhibition of neuronal activity through direct membrane conductance rather than second-messenger signaling. Because chemogenetic actuators are not endogenous proteins, they are delivered by viral vectors—chiefly adeno-associated viruses (AAVs)—whose serotype selection, cell-type-specific promoters, and stereotaxic injection confer expression restricted to genetically defined neurons in a chosen anatomical region. Optogenetic workflows depend on genetic recombination of opsins, fluorescent proteins, and regulatory elements, viral delivery, and localized light stimulation to achieve spatial and cell-type specificity, but the need for implanted fibers limits access to deep structures and clinical translation (23).

of ion channel-based chemogenetics (11). Together, advances in receptor engineering—from third-generation DREADDs to next-generation chemogenetic ion channels—have greatly diversified the mechanisms by which researchers can influence neural circuits.

TARGETED DELIVERY OF CHEMOGENETIC ACTUATORS: VIRAL VECTOR STRATEGIES

The successful use of neural modulatory systems relies heavily on gene-delivery strategies. Since chemogenetic actuators are not endogenous proteins, viral vectors—particularly adeno-associated viruses (AAVs)—are used to express them in target neurons. These AAV vectors are well suited to this purpose as they infect post-mitotic cells, sustain long-term expression, and do not integrate into the genome (12). Different AAV serotypes display distinct cell-type preferences, making differentiated targeting possible. This can be further improved by specific promoters, such as CaMKII (Calcium/Calmodulin-Dependent Protein Kinase II) for excitatory neurons or GFAP (Glial Fibrillary Acidic Protein) for astrocytes (13,14).

Using serotype selection, promoter targeting, and precise stereotaxic injection of viruses, researchers can express chemogenetic actuators in a specific, genetically identified population of cells in a given anatomical location. Stereotaxic delivery of viral vectors, together with cell-type-selective genetic tagging, allows chemogenetic expression in a particular group of neurons within a certain brain region. In addition, retrogradely transported AAV variants make it possible to target neurons and their projections, not just their location (15). Recent progress in viral-vector engineering, such as improvements in AAV, lentiviral, and herpes simplex virus (HSV), has made

chemogenetic tools much more precise. These advances allow for a level of specificity and anatomical targeting that is hard to reach with traditional lesion methods or electrode-based approaches (16). Combining genetic targeting with customized viral delivery is a key method in chemogenetic experiments, ensuring that drug effects are limited to the targeted neural circuit (Figure 1).

CHEMOGENETICS AND OPTOGENETICS: COMPLEMENTARY STRATEGIES

Optogenetics and chemogenetics are two similar techniques that serve the same system but have different scopes and modulations. Optogenetics enables the initiation and cessation of neuronal firing in milliseconds through light-induced ion exchange by inducing rhodopsin expression (17). Short pulses of light can stop or start activity in the neural circuit (18). Unlike chemogenetics, it functions independently of how the body processes the drugs. In chemogenetics, the ligand's effect on the receptor, its half-life, and its activity are also important (9).

Optogenetics is more suitable for experimental designs where rapid circuit activation and inhibition, high-frequency stimulation, and controlled timing are required. Optogenetic systems also have some practical drawbacks. Due to the absorption and scattering of light in deep tissues, fiber-optic cable implantation is necessary in the region (19). This limits the naturalness of the behavior (20). This also limits its applicability in clinical settings. Long-term implants, power supplies, and the fact that the light source emits heat raise safety concerns, which is a subject of ongoing research (21). On the other hand, chemogenetic systems, because they do not require implantation, have fewer device-related safety flaws.

In practice, chemogenetic experiments can be designed to minimally influence behavioral patterns. The receptor ligand can be administered by injection, oral gavage, or by mixing it into drinking water (22). In this respect, it is an important strategy for long-term behavioral studies and monitoring of chronic responses, and modulation can be achieved without over-manipulation of behavior. In chemogenetics, the main limitation is timing. The response is affected by the pharmacological agent and how it is absorbed, cleared, or distributed.

Furthermore, DREADDs are distinguished by their mechanisms of action. The DREADDs activate G-protein signaling via second-messenger pathways and gene expression that brief optogenetic currents do not. Because of this, chemogenetic methods are especially useful for studying plasticity and long-term changes in circuits (23). Overall, optogenetics and chemogenetics should be seen as complementary tools. Optogenetics is best for fast, precise control, while chemogenetics offers simpler experiments, works well in deep brain areas, and allows for longer-lasting effects. When used together, they provide a range of control, from millisecond accuracy to hours-long influence, allowing researchers to choose the best method for their specific question (Table 1).

CHEMOGENETIC APPROACHES IN DISEASE AND BEHAVIOR RESEARCH

Chemogenetic systems are being used in an increasingly widespread approach to researching disease and neural circuit mechanisms. This is because chemogenetic systems offer the possibility of reversible control in a specific neural population, often without being in a race against time. The DREADDs are used to modify the activity of a specific pathway in a particular neural population and to observe or objectively record the resulting behavioral consequences through standardized behavioral tests. By enabling experimental setups such as the eradication of a neural population with minimal harm to surrounding populations, they allow for more targeted and better-defined results than chemical damage applications.

For example, in Parkinson disease models, one of the most intensively studied areas of the dopaminergic system and pathology is the basal ganglia. By chemogenetically exciting underactive dopaminergic neurons in these areas and altering the activity of related pathways, improvements in motor function have been observed (24–26). For instance, engaging Gs-coupled DREADDs in D1-expressing striatal neurons increases direct-pathway drive and mitigates motor impairments, illustrating the therapeutic logic of restoring pathway balance rather than broadly altering neurotransmission (26). In epilepsy models, inhibitory DREADDs have been used to reduce spontaneous seizure production from hippocampal and cortical overactive neurons (27,28).

In Alzheimer disease, transient stimulation of the basal forebrain has been shown to improve cognitive function. At this point, it was shown that applying the specific neural tone of the stimulated population could reverse the deficits (29). Taken collectively, these applications shift disease models from static descriptions to empirically testable systems where circuit dysfunction and symptoms can be directly correlated through manipulation.

Chemogenetics, by opening up a pathway for neuronal modulation through reversible and specific selection in the behavioral field, has contributed to behavioral neuroscience. In this way, vital issues such as nutrition, affect, motivation, and reward, which are also relevant to neuropsychiatry, are able to be explored in greater depth.

Table 1. The comparison of major chemogenetic platforms and optogenetic neuromodulation.

Platform	Actuator/stimulus	Main mechanism	Temporal profile	Main advantage	Main limitation
RASSL	Engineered GPCR + synthetic ligand	GPCR signaling	Minutes-hours	Historical foundation of receptor engineering	Basal activity and limited ligand selectivity
DREADD	Engineered GPCR + designer ligand	Gq, Gi, Gs, or related signaling	Minutes-hours	Prolonged, minimally invasive modulation	Ligand pharmacokinetics and limited temporal precision
KORD	Engineered κ-opioid receptor + salvinorin B	Gi signaling	Minutes-hours	Multiplexed bidirectional control	Requires a separate ligand system
PSAM/PSEM	Chimeric ligand-gated ion channel + PSEM	Direct ionic conductance	Faster than GPCR-based systems	Rapid excitation or inhibition	More restricted actuator-ligand repertoire
Optogenetics	Opsin + light	Direct ion conductance or pumping	Milliseconds	Precise temporal control	Implantation, light penetration, and heating limitations

RASSL: Receptors activated solely by synthetic ligands, **DREADD:** Designer receptors exclusively activated by designer drugs, **KORD:** κ-Opioid receptor DREADD, **PSAM/PSEM:** Pharmacologically selective actuator module / pharmacologically selective effector molecule, **GPCR:** G protein-coupled receptor, **Gq, Gi, Gs**: G protein signaling classes.

For example, a chemogenetic study in hypothalamic circuits revealed a novel circuit pattern in hunger signaling, showing that activation of agouti-related peptide (AgRP) neurons promotes eating even during satiety, while their inhibition suppresses eating behavior. Conversely, chemogenetic activation of pro-opiomelanocortin (POMC) neurons, which are a modulatory nucleus within the arcuate network, promotes satiety (30).

Furthermore, the chemogenetic approach has also played a significant role in exploring how specific neuronal populations of specific neurotransmitters are involved in emotional and motivational processes. Activation of serotonergic dorsal raphe nuclei was found to enhance anxiety-like behaviors in different paradigms. The context-dependent nature of this response was indicative of bidirectional modulation (31). Silencing dopamine neurons in the ventral tegmental area (VTA) produces behavioral phenotypes such as decreased motivation, while excitation can increase reward seeking and link dopamine dynamics to goal-directed drive (32).

Although chemogenetic applications generate slower modulation compared to optogenetic systems, they offer advantages such as better performance in deep structures, providing robust and reversible modulation, and not requiring implanted fiber and cabling for modulation. This genetically tagged and pharmacologically flexible combination provides mapping of a specific neural circuit, recording of its behavioral outputs, and their processing within a disease-specific framework.

In short, chemogenetic systems combine molecular biology, genetic engineering, and neuroscience principles and allow for observation of the behavioral responses of functional neural networks in living models through manipulations. As vector platforms, ligand design, and targeting strategies continue to mature, chemogenetics is likely to remain a core methodology for circuit neuroscience and a conceptual scaffold for future, less invasive neuromodulatory therapeutics.

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