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**Review Paper**

# Exploring Brain Receptors: Key Players in Neural Signaling - A Systematic Review

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## ABSTRACT

This review article consists of the functions of opioid receptor binding sites, mainly focusing on mu, kappa, and delta receptors, exemplifying their characters and binding affinities, utilizing a least squares non-linear regression curve fitting program that provides insights on the interaction between opioid and their subtypes. And glutamate receptors particularly the mGlu5 receptor and their role in modulating behaviour and neurobiological responses to substances like amphetamine in preclinical and clinical study. Further of the side effects of cannabis on autism symptoms revealing promising outcomes with observable improvements in various domains and around 4% reported side effects. Overall, this systematic review contains the basic information on all the receptors present in the brain including their subtypes, their location, and function. Information of opioid, glutamate and cannabis receptors in detail.

***Keywords:*** *Opioid Receptor, Amphetamine Sensitization, mGlu5, Autism, Cannabinoid*

Receptors are chemical structures composed of proteins, present on cellular membrane. They interact with a specific ligand (primary messenger) that triggers a defined response through secondary messengers G-protein coupled receptor (GPCR) or ion channels (ligand-gated ion channels) (1). Receptors in the brain play a crucial role as they act as the target sites for neurotransmission (2). Neurotransmission is the transfer of information between neurons. Neurons are the cells in the brain that are responsible for receiving and transferring signals. The exchange of signals between neurons and nerve cells can be via both chemical and electrical impulses. Electrical signals, carried by charged particles within the neuron, facilitate rapid conduction from one end of the cell to the other. Neurons communicate through minute openings known as synapses, where certain parts of two cells (presynaptic and postsynaptic neurons) come within nanometers of one another to facilitate the transfer of chemicals. A chemical (neurotransmitter) that is released by presynaptic

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neurons is received by a postsynaptic specialized protein known as neurotransmitter receptor (3).

The brain contains various types of receptors that play a major role in receiving and transmitting signals.

- **Neurotransmitter receptors**

It is a membrane receptor protein that is activated by neurotransmitters and is located on the surface of neuronal and glial cells. There are two main types of neurotransmitter receptors: ionotropic and metabotropic (4,5).

**Ionotropic receptors:** they are ligand-gated ion channels, that are activated when the neurotransmitter binds with the receptors, which further leads to the opening of the receptor channels and influx of ions such as $Na^+$, $K^+$, or $Cl^-$ (6). They can be present anywhere in the neuron but are mainly located in the dendrites (7).

**Metabotropic receptor:** these receptors initiate various steps to alter cell activity and are activated by specific chemical ligands (8,9). Metabotropic receptors are all G protein-coupled receptors (GPCR), G protein activates a secondary messenger when the ligands bind which can affect the ion channels, regulate other proteins in the cell and alter the gene transcription (10,11). These receptors have a long-lasting effect (12). They are located on glial cells postsynaptically and perisynaptically and intracellularly they are present on the nuclear surface, endoplasmic reticulum and the intranuclear compartment (13).

***Major classes and examples of neurotransmitter receptor***

**Adrenergic receptors:** they are cell surface glycoproteins, a class of GPCR, they bind with catecholamines like noradrenaline and adrenaline which are released from sympathetic nerve endings that further stimulate the sympathetic nervous system (fight or flight), variety of responses such as smooth muscle contraction, blood pressure homeostasis and cardiac contraction are seen. Blockage of these receptors leads to various cardiovascular disorders like hypertension, angina pectoris or congestive heart failure (14). Adrenergic receptors are classified as alpha or beta receptors, these two are further classified as alpha -1, alpha-2, beta-1, beta-2, and beta-3 (15).

- **Alpha-1 adrenergic receptors** are postsynaptic alpha receptors found in smooth vascular muscle and they measure venous capacitance and arteriolar resistance along with BP. Phenylephrine is used as a vasopressor and oxymetazoline as a decongestant they are FDA-approved alpha-1 receptor agonists.
- **Alpha-2 adrenergic receptors** are found in the periphery and brain. In the brain, they regulate sympathetic outflow and may contribute to both sympathetic and regional blood circulation in the periphery. Methyldopa is used to treat hypertension and clonidine is used to treat attention deficit hyperactivity disorder they are FDA approved alpha-2 receptor agonists (15,16).
- **Beta-1 adrenergic receptors** are found in the cerebral cortex of the brain, heart, kidney and fat cells (17). It is a GPCR communicating through the Gs alpha subunit. A cAMP-dependent pathway is initiated through adenylyl cyclase by signaling the Gs which results in the potentiation of the receptor's function. In the heart, activation of beta-1 receptor increases atrioventricular nodal, sinoatrial nodal and ventricular muscular firing which further increases contractility and heart rate. In kidney, the beta-1 receptor upregulates

lipolysis (18). Dobutamine is used to treat heart failure and cardiogenic shock, it is used to increase cardiac output if the patient has organ perfusion and low tissue (16).

- **Beta 2 adrenergic receptors** are primarily located in airway smooth muscles. They can also be found in uterine muscles, cardiac muscles, mast cells, mucous glands, epithelial cells, vascular endothelium, lymphocytes, and skeletal muscles**.** Activation of the beta-2 receptor causes the Gs protein of the alpha subunit to separate and reconnect to adenylate cyclase, initiating it to catalyze the transformation of cAMP from adenosine triphosphate. Beta-2 receptor agonists are mainly used to treat respiratory disorders. They are further classified as short-acting drugs, long-acting drugs, and ultra-long-acting drugs.

  Short-acting drugs: ibuterol, metaproterenol, terbutaline, and levalbuterol and used to treat COPD and bronchial asthma.

  Long-acting drugs: arformoterol, salmeterol, and formoterol are used to treat patients with chronic bronchitis,COPD and emphysema.

  Ultra-long-acting drugs: recently a clinical trial has started for ultra-long-acting agonists to study their effects on asthma and COPD. Olodaterol is an example (19).
- **Beta 3 adrenergic receptors** are selectively found in brown adipose tissue in rodents and newborn humans (17).

**Dopaminergic receptors:** these receptors play a major role in daily life functions; they affect emotions and movement. They are present mainly in the central nervous system exactly in the subventricular zone and hippocampal dentate gyrus, also found in the periphery but more prominent in the kidney and vasculature. Dopamine is a hormone and monoamine catecholamine neurotransmitter; the function of dopamine depends on the type of receptor it binds with. The following are types of dopaminergic receptors: D1, D2, D3, D4, and D5 (20).

- **D1:** they are mainly found in the brain, with the highest levels in the nucleus accumbens, olfactory bulb, substantia nigra reticulata and caudate putamen and lower densities in the hippocampus, cingulate cortex, prefrontal cortex, and habenular of the brain (21). Following are the functions: memory, impulse control, locomotion, and regulation of renal function (20).
- **D2:** they are found post-synaptically on non-dopaminergic neurons and terminals of dopamine neurons, they regulate various brain functions, mainly cognition, motivation, and locomotion. D2 receptors are important for pharmacological targets for psychiatric diseases. And are also found at a lower extent in the amygdala, hippocampus, cortical region and hypothalamus and at higher density in the nucleus accumbens, striatum and olfactory tubercle (22).
- **D3:** they have post and pre-synaptic localization in brain stem nuclei, cortex and limbic parts of striatum and are found in hormonal, sensory and association regions such as cortical nuclei of amygdala, nucleus basalis, basomedial, basolateral, mediodorsal, anteroventral and geniculate nuclei of thalamus. They are involved in the motor functions, cognition, impulse and sensitization process (23,24).
- **D4:** it is a synaptic neurotransmitter in charge of neuronal signaling of the brain in the mesolimbic system they are found in the cerebral cortex, thalamic reticular nucleus, hippocampus and substantia nigra (25,26).
- **D5:** they are present in the hypothalamus, cerebral cortex, striatum, nucleus accumbens, substantia nigra-pars compacta and olfactory tubercle. They are involved in the modulation of psychostimulant-induced locomotion, cognition, renin secretion and decision-making (20,27).

**GABAergic receptor (gamma-aminobutyric acid):** it is an amino acid that serves as the CNSs main inhibitory neurotransmitter, it inhibits the nerve transmission that lowers the excitability of neurons. It is found in the hippocampus, thalamus, hypothalamus, brainstem and basal ganglia. When GABA is released into the post-synaptic nerve terminal the GABA receptors respond, they are the chief inhibitory receptors of CNS. GABA mediates its action through 2 types of receptors: inotropic $GABA_{A,}$ $GABA_c$ and metabotropic $GABA_B$ receptor (28).

- **$GABA_A$ receptor:** it is a ligand-gated chloride channel that is made up of a pentameric combination of various subunits. They are significant drug targets for the treatment of anxiety, epilepsy, insomnia, eating disorders, autism and bipolar disorder. It is localized in the CNS and post-synaptic sites of the brain (29). Benzodiazepines, barbiturates, anesthetics, neuroactive steroids and convulsants are the drugs being used to modulate anxiety, excitability, vigilance, memory, learning and circadian rhythms (30).
- **$GABA_B$ receptor:** it is metabotropic receptor that produces prolonged and slow action through G proteins and is broadly expressed in the nervous system and can alter neuronal excitability. They mediate their action by inactivating $Ca^{2+}$ channels, activating $K^+$ channels and inhibiting adenylate cyclase (31).
- **$GABA_C$ receptor:** It's an oligomeric protein complex found in various parts of the brain (32). They play a major role in segregation of other receptors, activation and contribute to multi neuronal pathway (33).

**Glutamate receptor:** it is a major excitatory neurotransmitter in the central nervous system, that connects the principal regions of the brain and localized on the neuronal and non-neuronal cells (34). They regulate their processes in brain, retina, spinal cord and peripheral nervous system. They are divided as follows: AMPA receptor, kainite receptor and NMDA receptor (35).

- **AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors:** they are widely distributed in the CNS, and play major role in memory and learning. They are central to regulating excitatory synaptic transmission. AMPA receptor subunits: GluA1, GluA2, GluA3 and GluA4 (36).
- **Kainite receptors:** they are expressed postsynaptically and presynaptically throughout the brain and mediate and modulate the neuronal circuitry in both pre and post-synaptic sites of specific neurons. Kainite receptor subunits: GluK1, GluK2, GluK3, GluK4 and GluK5 (37, 38).
- **NMDA receptor:** it is a primary excitatory neurotransmitter in the brain, plays an important role in synaptic plasticity and their neuronal mechanism is the basis of the formation of memory. They are present within the hippocampus, which plays a crucial role in memory formation. They are also present in glial cells and astrocytes to support neurons. NMDA receptor subunits GluN1, GluN2A-GluN2D, GluN3A and GluN3B (39).

**Glycine receptor:** they are ligand gated chloride channels that mediate rapid inhibitory neurotransmission in the brainstem and spinal cord. They are present from the early stages of brain development and are mainly found in the upper region of CNS and mediate synaptic neurotransmission (40).

**Histamine receptors:** they are GPCRs localized in sensory nerves, lungs, CNS, gastrointestinal smooth muscle, adrenal medulla, heart and immune cells. They play a major role in controlling the gastric acid secretion and pathophysiological role in allergic disorders. They are further subdivided into $H_1$, $H_2$, $H_3$ and $H_4$ receptors (41).

- **H1 receptors:** they are present in the lungs as they mediate bronchoconstrictive effects and increase vascular permeability and are present on B cells, T cells, monocytes and lymphocytes, stimulation of these induce pro-inflammatory effects (42).
- **H2 receptor:** they are present in brain, exocrine and endocrine glands, cardiovascular system, pulmonary system, gastrointestinal muscle, genitourinary and immunological system. Activation of these receptors leads to increase in intracellular cyclic AMP with increased activity of adenylate cyclase (43).
- **H3 receptors:** it is found throughout the CNS including hippocampas, cerebral cortex and striatum. H3 receptors inhibit the release of histamine, impulse flow along the neurons and synthesis of histamine (44).
- **H4 receptor:** they are present in the haematopoietic cells that play a role in inflammation and allergy also linked with colon cancer, rheumatoid arthritis and breast cancer (45).

**Cannabinoid receptor:** are GPCSs and play a major role in metabolic regulation, anxiety, pain, bone growth, craving and immune function. They respond to cannabinoids and endocannabinoids (46). They are abundant in the brain and are important in producing various psychoactive effects. They are further classified as cannabinoid receptor type 1 (CB(1)) and cannabinoid receptor type 2 (CB(2)) (47).

- **CB(1):** they are present in the brain and peripheral sites and primarily localized in the cell membrane. They mediate the psychoactive effect of cannabinoids.
- **CB(2):** mostly expressed in CNS, peripheral immune system, pyramidal neurons, and glial cells. And are involved in immunosuppressive and anti-inflammatory actions (48,49,50).

**Opioid receptors:** are GPCRs that mediate the response of the body to various hormones, drugs, and neurotransmitters and are also involved in olfaction, vision and taste. They are present in respiratory center, ANS, cardiac tissue, cerebral cortex, peripheral chemo, thalamus, and baroreceptors. There are 5 types of opioid receptors: mu receptor (MOR), kappa receptor (KOR), delta receptor (DOR), nociception receptor (NOR) and zeta receptor (ZOR) delta receptor is further divided as delta1 and delta2 (51).

- **Mu receptor (MOR):** they are present in the CNS, expressed in the dorsal horn of the spinal cord and various regions of the brain that are involved in processing painful information and localized in the GI tract where they are responsible for opioid-induced constipation effect (52). Mu receptor (MOR) is further divided into mu1, mu2, and mu3.
- **Kappa receptor (KOR):** they are widely spread throughout CNS and modulate the physiological processes based on their location and are present within the GI tract, heart, respiratory system, immune cells, and terminals of sensory nerves. Kappa receptor (KOR) is further divided into kappa 1, kappa 2 and kappa 3 (53).
- **Delta receptor (DOR):** they are protein's called receptor present on nerve cells, mainly in parts of brain and spinal cord related to mood reward, and pain regulation (54) they play major role in other physiological processes like mood regulation, stress response and addiction (55,56).

## MATERIALS AND METHODS

**Search strategy:** the information is collected from various databases such as PubMed, Web of Science, Google Scholar, Scopus, Science Direct, Medline and neuroscience research.

**Inclusion criteria**

a. **Opioid receptor:** samples of brain tissue were taken from deceased patients; it was obtained 3-5 hours after their death. The subjects ranged from age 16-66 years. Use of titrated ligands in binding experiments, tissue homogenized with ultraturrax, and least squares non-linear regression curve fitting program for data analysis (57).
b. **Glutamate receptor: Mice**: For all rodent trials, male C57BL6 mice that were between two to six months old were used. Including Wild-type mice and knockout mouse models. Mice meet the required health criteria for experiment suitability and are based on behavioral characteristics according to the goals of the study. **Human:** healthy volunteers were considered to be mentally and physically stable. Individuals ready to follow the instructions like taking the drug and attending imaging sessions and undertaking PET scans were considered for the study (58).
c. **Cannabinoid receptor**: this review includes articles published until October 2020, in any language, or the form of clinical trials or case studies involving human beings. A total of 9 articles were included in the review. The articles were selected based on their title, abstracts, and the screening process (59).

**Exclusion criteria**

a. **Opioid receptor:** samples of brain tissue not taken from people with brain diseases or traumas or whose postmortem intervals were beyond the predetermined range and the samples that were stored or handled incorrectly. Samples that were too small, were collected unethically. And if there was any past medications would affect the binding assay results were not considered (57).
b. **Glutamate receptor**
   **Mice:** the mice with underlying abnormalities or illnesses that may have an impact on the resulting outcome and the ones that do not fit in the study and genetic parameters are not considered. Mice that are used for previous experiments are not considered as it could impact the response. **Human:** individuals with psychiatric or medical could affect the results or even put the participants at risk during drug administration. Individuals who are nursing, pregnant, who are on other drugs who cannot undergo PET scans or other imaging procedures, and the ones incapable of following the protocol are not considered for the study (58).
c. **Cannabinoid receptor:** the articles that did not show the effect of cannabis on autism symptoms were not included. Research irrelevant to the review goal was not considered, articles with only abstract and no full-text content were excluded, and studies involving only animals were not considered (59).

***Study design***

**a. Opioid receptor**

**Preparation**: Five brains were obtained from five subjects: three males (age 33 to 45 years) who died due to heart attacks; a 66-year-old lady; and a 16-year-old girl who died from acute alcohol poisoning. The brains were collected within 3.5–5.5 hours of the death, they were extracted and frozen at -70 °C.

**Experiment design**: Brain tissue was defrosted, homogenized in 30 liters of Tris buffer (pH 7.4, 50 mM) using Ultraturrax, and centrifuged for 20 minutes at 40,000 g. After discarding

the supernatant (54) the pellet was again suspended in the buffer and centrifuged in the same manner. The tissue was suspended in 100 or 200 (original tissue weight: volume) volumes of the assay buffer for the binding tests. Tris Krebs ringer buffers pH was adjusted to 7.4 and Ringer buffer with the following composition (in mM) was used: NaC1, 118; KC1, 4.75; MgSO4, 1.2; CaCI2, 2.54; Tris, 50 (57,60).

In polypropylene tubes, tritiated ligands were incubated (0.1 ~3.5 nM) with the homogenate and the unlabeled ligands for 40 min at 35 °C. Increasing quantities of unlabeled ligands were added to create competition curves. Each concentration was done in a duplicate tube. As previously mentioned, the fast filtration method was used to separate the bound- from free-ligand (62).

**b. Glutamate receptor**

**Preparation**

**Mice:** Male C57BL6 mice (2-6 months), tissues were collected from three wild-type mice, one mGlu5 knockout mouse, and one transgenic mouse. **Human:** 19 healthy volunteers 14 women and 5 men (58).

**Behaviour assessment**

1. **AMPH (amphetamine) sensitization in mice**: In mice, two Amph sensitization regimens were employed: a 3-dose pretreatment regimen meant to approximate the comparatively mild sensitization effects anticipated in people, and a 5-dose pretreatment regimen more in line with those observed in the body of current literature. As previously mentioned, 2mg/kg of Amp or saline (i.p.) to the mice once a day for 3 days (n = 15 for saline, n = 12 for Amph) or 5 days (n = 12 each group). A 6-day delay followed the induction phase. After seven days of induction, mice received the same treatment they had previously been given (2 mg/kg Amph or saline). In the fifth group, three injections of saline pretreatment were administered along with a challenge dose of Amph to six mice. Every step was conducted throughout the light cycle, and following each dosage, locomotor activity was assessed. Between 1400 and 1600 hours, following the last behavioral session, the animals were instantly put to death. Their brains were removed, frozen at -30°C in 2-methylbutane, and then kept in storage at -80°C (58).
2. **AMPH sensitization in humans:** in this study, the participants are administered with amphetamine or a visually identical placebo. They received the drug or placebo in 3 sessions that were 48 hours apart. Subjective reactions, blink rate, motor responsiveness, speech rate, and physiological reactions were measured after 2.5 hours following the administration. After 3 weeks following the initial dose individuals were again given the same medicine that they received initially. Greater response of sensitization was seen when compared to day one, anticipated sensitization in motor tests and on self-reported activity and energy level measurements (visual analog scales [VAS]), based on prior research, measuring energy, alertness, and a racing mind), but not on conscious motivation metrics (VAS measuring drug liking, desire to take again) or euphoria/high (VAS measuring excitement, high and rush); based on earlier research, some effects included changes in energy levels, motor measure and self-reported activation measure based on the visual analog scales and no sensitization was seen (63).
3. **Quantification of mGlu5**

   **Mice autoradiography**: One mGlu5-KO mouse and freshly preserved brains of mice that underwent behavioral testing were cut at a 12 mm thickness on a slide-mounted cryostat kept at -80°C. With a few minor adjustments, and conducted autoradiography (64).

4. **PET scan in humans:** the individuals underwent PET scan on the 1st day and 21st day. The scan was done between 10:00 AM – 01:30 PM followed by immediate pill administration. The MRI scans were performed separately. A PET scan was conducted on the 3rd and 5th day to reduce the procedural stress on behavior measurements. During these scans the participant had a venous catheter inserted and for 66 minutes there was no data collection. The synthesis of [11C] ABP688 was carried out as previously mentioned. And started a 60-minute dynamic transmission scan after a 6-min transmission scan at 137Cs to account for tissue attenuation. Concurrently a catheter was inserted into the antecubital vein, administering a 1-min injection of 369 ± 29.1 MBq [11C] ABP688 (92 ± 3.8% [E]-isomer). Gathered list-mode data and rebuilt it according to the earlier explanation. The mean regional binding potential (BPND) values for 10 grey matter regions of interest were calculated using the simplified reference tissue model 35 with cerebellar grey matter as a reference. The researchers then used SPM12 to compare the voxel-wise BPND values within each treatment group from 1st day to 2nd day (62,65).

**c. Cannabinoid receptor Subject and method:**

Types of Cannabis Product Employed: Five studies have used CBD (cannabidiol)-rich oil, with differences in the ratios of THC (tetrahydrocannabinol) and CBD. Two studies used Oral CBD solution, dronabinol in one investigation, and cannabidivarin (CBDV) in one investigation. Dosage: The ratio of CBD to THC in CBD-rich oil ranged from 1-1.5% THC and 6-75% CBD, 600 mg of pure dose. The daily doses of dronabinol ranged from 0.62 to 3.62 mg, and the amount of CBDV was 600 mg. Children, adults, and adolescents were included in the study some cases the age group wasn't specified. The imaging technique study was conducted only in three instances others were evaluated based on subjective reports and questionnaires. In one study the subjects were randomized to receive either placebo or CBD, where half received placebo and the other half received CBD. Two studies used a method known as randomized, double-blind, placebo-controlled trials. Randomly assigning participants, blinding both the researchers and the subjects, and incorporating a placebo control group. And the other studies the intervention of cannabinoids or cannabis was given without randomization (59).

**Opioid receptor data analysis:** The least squares non-linear regression curve fitting program used has been described. It offers an estimate of binding capacities and affinities (Ka) that fit well in the experimental points and are based on the law of mass action. The models which assume two or three binding components, comparing the goodness of the curve with the data. An F-test is used to select a suitable binding model and examination of several curves is acquired by different combinations of labeled and unlabeled ligands. Estimation of binding parameters is possible by this method (57).

## RESULT

**a. Opioid receptor**

**Binding characteristics of Dihydromorphine (μ-receptor agonist):** binding sites tagged with [3H] dihydromorphine possess an equilibrium dissociation constant (Ka) of 0.7 ± 0.3Nm. different opiate ligands exhibited a stronger affinity for [3H] dihydrmorphine displacement indicating their interaction.

**Binding characteristics of DADL (D-ala2-D-leu5-enkephalin) delta opioid receptor agonist:** binding sites tagged with DADL had an apparent Ka of 1.3 ± 0.2Nm. the delta ligand exhibited more intricate competition curves indicating their involvement with other binding sites and different opioid ligands moved away from one binding site.

**Binding Characteristics of Ethylketocyclazocine and SKF 10,047 (κ-receptor agonists):** one apparent binding site was completely removed by unlabelled ethylketocyclazocine and SKF 10,047 displacing [3H] ethylketocyclazocine and [3H] SKF 10,047. Flat and biphasic curves of DADL indicate interaction with several binding sites. Binding characteristics of diprenorphine (non-selective opiate agonist): A homogeneous population of binding sites with a Ka of 0.22 ± 0.03nm was tagged by [3H] diprenorphine. The competitive curve of ethylketocyclazocine against [3H] diprenorphine shows interaction with multiple binding components.

**Complex competition curves with DADL and DAGO against diprenorphine:** these curves were flat and multiphasic indicating interaction with various binding components (57).

**b. Glutamate receptor: Behavioural sensitization to Amph in human and mice**

**Locomotor response in mice:** When compared to the reactions to dosage 1 administered with three prechallenges, the response of the locomotor activity to the final dose was significantly larger.

**Psychoactivating outcome of Amph in humans:** After the fourth dosage of the medication, there was an increase in speaking rate but no change in the placebo. The medication treatment did not impact the rate at which the eye blinks. The main effects of the treatment were observed in feelings of euphoria and alertness but not in conscious motivation and anxiety. However, the plasma Amph increased heart rate, blood pressure, and blood cortisol level, however it remained constant during sessions.

***Changes in mGlu5 with Amph sensitization***

**mGlu5 binding in mice:** the study examined [3H] ABP688 binding sites which are showing the presence of mGlu5 receptors. The specificity was confirmed when it was found that these binding sites were absent in the brain sections of the mice lacking the mGlu5 receptor and in the presence of a particular mGlu5 antagonist called MPEP confirmed the specificity of the ligand. Coral slices were used to detect [3H] ABP688 binding sites and was discovered that the distribution of the receptors is similar in humans and mice. Mice pretreated with 3 doses of Amph, no difference was observed. Compared to controls treated with saline, animals given five doses of Amph prior to treatment exhibited a noteworthy decrease in the binding of mGlu5 in the dorsal striatum.

**Availability of mGlu5 in humans:** the study used positron emission tomography (PET) to evaluate the binding availability. It was found that men have, on average, 26% higher bonding potential than women. There were no significant alterations in the accessibility of mGlu5 binding across the brain.

***Correlation analyses of the relationship between mGlu5 and behavioral sensitization***

**Post Amph availability and locomotor sensitization in mice:** it was found that they are unfavorably correlated with the initial drug response and extent of locomotor sensitization. It shows that alteration in the mGlu5 availability in the nucleus and dorsal striatum may play a role in modulating the response of Amph and the development of locomotor sensitization.

**Post-Amph psychomotor sensitization and mGlu5 availability in humans:** There were no changes found from 1$^{st}$ to 21$^{st}$ day. However, on 21$^{st}$ day, the changes in mind ratings was negatively correlated with BPND. This suggests that the higher availability of mGlu5 in the

dorsal striatum, and prefrontal cortex, cingulate and insula will exhibit less increase in mind racing following Amph administration. As we delve deeper BPND increased in non-sensitizers and not in sensitizers, this shows that individuals with less tendency for behavioral sensitization experienced a drug-induced increase in mGlu5 availability (58).

c. **Cannabinoid receptor:** Improvement was shown in the ASD symptoms such as: self-mutilation, hyperactivity, rage, sleep issues, restlessness, anxiety, psychomotor agitation, aggression, irritability, sensory sensitivity, cognition, social interaction, attention, language change and depression, have improved in studies testing cannabis.

Some side effects that were monitored: Sleep disturbances, restlessness, anxiety, changes in appetite, moderate irritability, increased appetite, diarrhea, behavioral issues, conjunctival hyperemia diminished cognition, exhaustion, and aggression/agitation were among the small percentage of people (2.2% to 14%) who experienced side effects from cannabis products. In a single-case investigation, a youngster developed psychotic symptoms. The symptoms were relieved after nine days when ziprasidone was administered instead of CBD and THC (59).

***Table no 1: Review of Literature***

| Author | Title | Study Outcome | Journal Name |
|---|---|---|---|
| ***Pfeiffer et al., (***1982) | Opiate Receptor Binding Sites in Human Brain | The study explores the how opiate ligands bind in the sites of human brain by performing heterologous displacement experiments with combinations of radiolabeled and unlabeled putative prototype opiate ligands (57). | Brain Research |
| ***Gramsch et al.,*** (1979) | Regional distribution of methionine-enkephalin- and beta-endorphin-like immunoreactivity in human brain and pituitary. | The study found concentrations of immunoreactivities such as methionine-enkephalin and β-endorphin in 33 regions of the human brain and pituitary.The distribution pattern of both varies greatly, implying that both endorphins exist in the central nervous system independently. No overall difference was seen in the concentration of endorphins in alcoholics and opiate dependent patients as compared to natural history cohort (58). | Brain Research |
| ***Pfeiffer et al.,*** (1981) | Demonstration and distribution of an opiate binding site in rat brain with high affinity for ethylketocyclazocine and SKF 10,047, Biochem | Based on the findings of pharmacological studies, different classes of opiate receptors are proposed. Three distinct rat brain regions were used to determine how the opiate ligands interacted with μ-, κ-, σ- and δ-binding sites. A technique called computerized curve fitting was used to analyse the data. The data implied that 3 classes of opiate binding site existed. Two of them displayed characteristic of μ- and δ-binding site in terms of distribution and affinity. The third site (R3) had high affinity towards σ- and κ-binding sites and low affinity towards μ- and δ- binding site. R3was to | Biochemical and Biophysical Research Communications |

| Author | Title | Study Outcome | Journal Name |
|---|---|---|---|
| | | resemble the distribution pattern of μ-binding site but were different from δ-site (73). | |
| ***Pfeiffer et al.,*** (1982) | Discrimination of 3 opiate binding sites with the use of a computerized curve fitting technique, Molec. Pharmacol | This paper offering a thorough analysis of opiate receptor binding locations using advanced computational techniques, improving our knowledge of opiates' pharmacology while potentially influencing opiate receptor-related future research and treatment plans (75). | Molecular Pharmacology |
| ***Smart et al.,*** (2021) | Metabotropic glutamate type 5 receptor binding availability during dextroamphetamine sensitization in mice and humans | The findings of the study suggest that changes in the availability of mGLU5 are not considered for the initial neural adaptation in stimulant-induced behavioral sensitization, although low mGLU5 binding may indicate a greater susceptibility to sensitization (58). | Journal of Psychiatry and Neuroscience |
| ***Robinson et al.,*** (1993) | The neural basis of drug craving: an incentive-sensitization theory of addiction. | The study reported about the biopsychological theory of drug addiction and the Incentive-Sensitization Theory (61). | Brain Research |
| ***Boileau et al.,*** (2006) | Modeling sensitization to stimu lants in humans: an [11C] raclopride/positron emission tomography study in healthy men | In this work, PET/[11C]raclopride imaging is used to validate an experimental model of stimulant-induced sensitization in healthy men. They discover that increased dopamine release in the striatum as a result of repeated stimulant administration indicates neurochemical sensitization. This discovery highlights the part that dopamine dysregulation plays in the mechanisms underpinning addiction and psychosis (62). | JAMA Psychiatry |
| ***Robinson et al.,*** (1986) | Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. | The study reports that when a moderate to high dose of AMPH is injected, it produces hyperdopaminergic state brain and behavioural changes associated with a schizophrenia like disorders. It suggests there is possibility that elevated concentration of DA at synapse is reason behind paranoid schizophrenia and amphetamine psychosis. Although lower doses of AMPH do not produce such changes but when administered intermittently and repeatedly can produce high concentration of DA this is due to enhanced relase of DA. This increased DA release in non humans I manifested as behvioural sensitization and AMPH psychosis in humans (63). | Brain Research |

| Author | Title | Study Outcome | Journal Name |
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| ***Sakae et al.,*** (2015) | The absence of VGLUT3 predis poses to cocaine abuse by increasing dopamine and glutamate sig naling in the nucleus accumbens. | This study proves that VGLUT3 reduces cocaine-induced behaviour by modulating glutamate and DA transmission in the NAc. It has been previously recognized that TANs from NAc are key modulators of reward behaviour and cocains reinforcing quality. The mechanism of this is yet unclear but this study suggests that TANs utilize 2 distinct chemicals codes (ACh and glutamate) for communicating with the neighbouring neural network in NAc. It was observed that mice that lacked release of ACh in the NAc showed a decreased release of DA. Silencing the transmission of ACh in TANs had very little effect on TANs reward behaviours and the reduced DA transmission in VAChT -null mice did not result in reduced reward behavior. Further investigations need to be done on this topic (64). | Molecular Pharmacology |
| ***Cloninger et al., (***1993) | A psychobiological model of temperament and character. | This study talks about the psychological model taking into consideration the temperamental and character traits while describing the construction and evolution of personality. It has been previously confirmed that 4 temperamental trait inherited independently exist; novelty seeking. Reward dependency, danger avoidance and persistence and they present early in life and involve on preconceptual basis in habit formation and visual memory. For the first time the three aspects of character that develop during adulthood and possess influence on social and personal effectiveness by development of self concepts. Self concepts differ depending on the extent to which and individual identifies. Every element of self concepts associates with one of the three aspect of character which are self-transcendence, self-directedness and cooperativeness (65). | JAMA Psychiatry |
| ***Young et al.,*** (1995) | A comparison of Tridimen signal Personality Questionnaire dimensions in bipolar disorder and unipolar depression. | Given that the HA personality dimension score was higher in both patient groups as compared to healthy volunteers, the findings of this study imply that HA personality dimension is not particularly related to UD but rather is associated with mood disorder generally. RD dimension observed no difference among the patient and comparison group. Although NS dimensions were | Psychiatry Research |

| Author | Title | Study Outcome | Journal Name |
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| | | elevated significantly in BD patients than in UD and comparison group (66). | |
| ***Hooks et al.,*** (1991) | Individual differences in locomotor activity and sensitization. | The study demonstrated that locomotory response to SCOP, cocaine and AMPH acted as a precursor to locomotory activity in an unknown environment. Rats that presented with elevated levels of locomotory activity in a novel environment also displayed significant responses to all three drugs. Additionally, a relationship has been established between the degree of locomotory activity on the $5^{th}$ day of cocaine and AMPH and locomotor response in an unknown environment (67). | Pharmacology Biochemistry and Behavior |
| ***Wardle et al.,*** (2011) | Quantifying talk: developing reliable measures of verbal productivity. | The study identified two distinct processes after learning about the different forms of talkativeness. One process is associated with comparatively unstructured speech and the other relates to a speech generated to achieve an objective or goal. This study provides the groundwork for further research driven by a hypothesis that examines the underlying factor structure of verbal output and investigates various components of talkativeness like social, psychomotor and cognitive and also measures the effect of medication and other environmental variables on speech (68). | Behaviour Research Method |
| ***Willeit et al.,*** (2016) | Imaging the effects of d-amphetamine in the human brain for modeling dopaminergic alterations in schizophrenia | The study reported that [$^{11}$C] –(+)-PHNO PET test is an effective tool for studying the effect of amphetamine and amphetamine-sensitized state. The similarities and differences between a natural amphetamine-sensitized state and amphetamine-sensitization in schizophrenia can be understood by analyzing the binding of [$^{11}$C] –(+)- PHNO in different subdivisions of dopamine (69). | International Journal of Neuropsychopharmacology |
| ***Silva et al.,*** (2022) | Cannabis and cannabinoid use in autism spectrum disorder: a systematic review. | Cannabis and cannabinoids have shown potential to have beneficial effects in treating the symptoms of ASD, and they could potentially be used as an alternative to relieve those symptoms. However, randomized, placebo-controlled, double-blind clinical trials need to be conducted to clarify the impact of cannabis and cannabinoids on patients diagnosed with ASD (59). | Trends Psychiatry Psychother |

## DISCUSSION

The experiments were performed to analyze the binding sites of the opioid receptors in the brain involving combinations of radiolabeled and unlabeled opiate ligands at mu, kappa, and delta sites. The obtained results were the approximations of the proportional affinities of different opioids in agreement with the concept of different locations for the mu, kappa, and delta. The presence of mu, kappa, and delta sites was identified through computer modeling in brain regions such as nucleus caudatus, gyrus cinguli, and area strata. This method helped estimate the distribution of mu, kappa, and delta sites in brain regions. The distinct features in the frontal cortex pointed to possible interactions between the kappa and delta sites (72). It was seen that ligands that interact with delta sites like dihydromorphine and DAGO went through a single high affinity binding, but DADL showed a strong preference for the kappa site (73). SKF 10,047 and ethylketocyclazocine both exhibit affinity for mu and kappa sites (74,75). The presence of immunoreactive dynorphin in certain brain regions corresponds with the distribution of delta sites indicating the function of dynorphin in regulating opioid receptor activity. There may be functional consequences to the distribution of opioid receptor subtypes (76).

This experiment describes the investigating availability of the mGlu5 receptors throughout the Amph sensitization in both rodents and humans. It was found that there were no statistically important changes in the accessibility of mGlu5 following the amphetamine regimen that was sufficient to induce behavioural sensitization (77). A more stimulant therapy caused the mouse striatum's mGlu5 receptor binding to reduce. These findings summarize that alterations in the availability of mGlu5 may happen with ongoing medication use but sensitization doesn't require them (78). Lower mGlu5 availability following the drug treatment was linked to increased amp-induced behavioural sensitization in rats and humans. Based on the study a minimum threshold required to bring about modifications to cause changes in the mGlu5 availability consists of 3-5 doses of amph. This also implies that the person susceptible to sensitization may be influenced by low mGlu5 activity also leading to amph addiction (79).

This review shows a decrease in the symptoms of ASD after using cannabis-based products. The available evidence is still not enough and more carefully planned clinical trials are essential to validate these results and demonstrate their effectiveness. Despite minor side effects like increased hunger, restlessness, and sleep disruptions evaluated in the studies, cannabis products seem to be comparatively safer than standard drugs, still, a long-term and thorough assessment is required in kids and teenagers with ASD. Of particular interest is the role of the endocannabinoid system in the pathophysiology of ASD (80). ASD is linked to the dysregulation of the system, which includes changed endocannabinoid levels. Still further research is required to clarify their underlying mechanism. Healthcare professionals should employ prudence and sound judgment while recommending cannabis-based medications to patients with ASD (81). This review also emphasizes the need for more investigation into the safety effectiveness and long-term impacts of cannabis which includes conducting bigger controlled trials, and functional and imaging assessments. While the preliminary studies suggest that cannabis-based products offer therapeutic effects still a lot of rigorous research has to be done to validate the facts (82).

The current study focuses on these 3 receptors namely opioid and its binding sites, binding of the metabotropic glutamate type 5 receptor during the sensitization of humans and mice to dextroamphetamine and study of cannabinoids in autism spectrum disorder. Further investigations can be carried out on the biomarker and antioxidant studies.

## CONCLUSION

In conclusion, this review article proves the function of opioid receptor binding sites and their characteristics it is mainly focused on the mu receptor, kappa receptor and delta receptor and their binding functions. The data from these receptors was analyzed using a non-linear regression curve fitting program based on the method of least squares, which provides estimates for the binding capacities and their affinities. As per the result obtained each opioid ligand interacts with the subtypes mu, delta and kappa with varying affinities. Dihydromorphine predominantly binds with the mu receptor, DADL to the delta receptor, and ethyketocyclazocine to the kappa receptor, each of which shows a specific Ka value. The displacement of labeled ligands by unlabeled ligands shows the competitive binding interactions where the unlabelled ligands compete for the same binding sites. The flat and multiphasic curves suggest heterogenicity at the binding sites. In glutamate receptors, the results suggest that mGlu5 receptors play a crucial role in modulating the behavior and neurobiological responses to Amph both in mice and humans. In the study examining the impact of cannabis on the indications of autism, it was proved that there were improvements in the range of symptoms including social interaction, attention, sensitivity, cognition, and depression. Most of the individuals benefited, but a small percentage of people (ranging from 2.2% - to 14%) reported adverse effects such as changes in appetite, anxiety, restlessness, and sleep disturbances.

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***Conflict of Interest***
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