Exploration of Neuroprotective Therapy

Open Exploration

Open Access Review

# Possible roles of heteroreceptor complexes in excitotoxic processes

Diego Guidolin[1]*, Cinzia Tortorella[1], Manuela Marcoli[2], Chiara Cervetto[2], Raffaele De Caro[1], Guido Maura[2], Luigi F. Agnati[3]

[1]Department of Neuroscience, University of Padova, 35121 Padova, Italy
[2]Department of Pharmacy, University of Genova, 16126 Genova, Italy
[3]Department of Biomedical Sciences, University of Modena and Reggio Emilia, 41121 Modena, Italy

***Correspondence:** Diego Guidolin, Department of Neuroscience, University of Padova, 35121 Padova, Italy. diego.guidolin@unipd.it

**Academic Editor:** Shile Huang, Louisiana State University Health Science Center, USA
**Received:** April 30, 2024 **Accepted:** August 14, 2024 **Published:** September 24, 2024

**Cite this article:** Guidolin D, Tortorella C, Marcoli M, Cervetto C, De Caro R, Maura G, et al. Possible roles of heteroreceptor complexes in excitotoxic processes. Explor Neuroprot Ther. 2024;4:366–91. https://doi.org/10.37349/ent.2024.00089

## Abstract

Excitotoxicity represents a neuropathological process, describing the toxic actions of excitatory neurotransmitters, where the excessive or prolonged activation of glutamate receptors triggers a cascade of events leading to neuronal injury or death. Under conditions of reduced energy availability and increased oxidative stress neurons become particularly vulnerable to excitotoxicity and a large body of available evidence indicates that excitotoxicity represents a central mechanism in the pathogenesis of acute and degenerative diseases of the central nervous system. Astrocytes represent key elements in the regulation of glutamate homeostasis by their opposing functions of glutamate uptake and release, and microglial cells play an important role in the response to damage. Depending on the phenotype they assume when activated, microglial cells can trigger immune defense or neuroprotective processes. To perform their functions both glial cell populations monitor the extracellular space through a panel of receptors. Furthermore, a variety of signaling pathways also contribute to the modulation of the glutamatergic transmission, acting on specific cell receptors expressed by neurons, astrocytes, and microglia. In the last decades, evidence has been provided that receptors of almost all families can establish structural receptor-receptor interactions, leading to the formation of heteroreceptor complexes at the cell membrane of neurons and glial cells. The cooperativity that emerges in the actions of ligands of the monomers forming these assemblies provides the cell decoding apparatus with flexible dynamics in terms of recognition and signal transduction and allows an integration of the incoming signals already at the membrane level. Available data on possible modulatory roles played by heteroreceptor complexes in excitotoxic processes will be here reviewed and discussed. From the pharmacological standpoint, these findings may offer possibilities to explore novel therapeutic strategies targeting receptor complexes to address disorders of the central nervous system associated with dysregulation of glutamatergic signaling.

## Keywords

Receptor-receptor interactions, receptor complexes, astrocytes, microglia, glutamate, excitotoxicity

## Introduction

Functional interactions between receptors, not requiring a physical contact between receptor molecules, have been often observed [1]. They may occur by sharing signaling pathways or by mechanisms of transactivation. In the 1980s, however, in vitro and in vivo experiments by Agnati, Fuxe, and collaborators [2–4] provided indirect biochemical and functional evidence that structural interactions between G protein-coupled receptors (GPCRs) could also be established, leading to the formation of receptor complexes (dimers or high order oligomers) at the cell membrane (see [5] for historical details). The term "receptor-receptor interaction" (RRI) later was proposed to indicate such an interaction between receptor proteins involving a direct physical contact [6]. In the years that followed, several groups (see [7] for references) provided direct evidence for the existence of this molecular organization by exploiting a set of experimental techniques able to detect the spatial proximity of protein molecules [8–11].

The basic molecular mechanism characterizing the receptor assemblies are allosteric interactions [12–15], allowing the transfer of the energy associated with conformational or dynamic changes at some site of a protein to other sites, that will change their conformational or dynamical features accordingly. Thus, when protomers establish direct RRI and form a quaternary structure, energy perturbations occurring at some site of a protomer can propagate over the interface between receptors into the nearby protomers, changing their conformational and functional properties and allowing a cooperative behavior of the complex [16]. The interface between protomers and the residues involved, therefore, significantly influence the overall architecture of a receptor complex and its behavior, representing a topic of great interest in current research on receptor oligomerization. In this respect, several bioinformatics methods have been devised to predict the available interfaces (see [17–19] for specific reviews). Concerning GPCRs, experimental results indicate that the number of ways they interact in the membrane to form complexes is actually limited, the vast majority of experimentally identified receptor complexes being dimers. In addition, some interfaces have been observed to be more exploited than others for RRI [20]. Transmembrane (TM) domains TM4 and TM5 or the intracellular loop 3, for instance, have been often experimentally identified as interaction interfaces between GPCRs [19]. Nevertheless, oligomeric heteroreceptors have been detected [20–24].

The organization of receptors as receptor complexes is of particular interest under a functional perspective, since they can modulate cell activity, as shown by studies on neurons [25], where they could modulate synaptic weight [26], most likely affecting learning and memory processes [27, 28]. The collective dynamics of these supramolecular structures, indeed, allows the integration of different incoming signals reaching the plasma membrane to initiate specific patterns of signal transduction [29].

In general terms, several oligomerization-dependent signaling modifications have been identified or suggested [30], as briefly illustrated in Table 1.

**Table 1.** Possible signaling changes following oligomerization

| Allosteric modulation | References |
|---|---|
| Modulation of protomers recognition | [31] |
| Receptor desensitization | [32] |
| Modulation of the downstream signaling cascade | [33, 34] |
| Emergence of novel allosteric binding sites | [35] |

In addition, increasing evidence [36] shows that responses to specific ligands are also critically influenced by the environment in which receptor complexes are located, including lipid domains, scaffolding proteins, and other biochemical partners [37].

The majority of the available studies on RRI have been focused on GPCRs, with specific regard to the central nervous system (CNS) [38–40]. Oligomeric organization, however, plays an important role in the function of all receptor families, with the ion channel receptors (where multimerization is necessary) being located at one end of the spectrum and GPCRs (able to signal as monomers or stable dimers, or to give rise

to transient quaternary structures [41]) at the other, indicating that it probably constitutes a general and efficient mechanism for modulating the functionality of receptor proteins [12, 30]. Furthermore, receptor multimerization was found to play a role in the physiology not only of nerve cells, but also other mammal cell populations [30, 42].

Based on these findings, a great research effort has been focused on two main pharmacological issues. On one hand, studies were directed at identifying dysfunctions or disruptions of receptor complexes that could represent a molecular basis for pathological changes associated with diseases [39, 43–47]. On the other hand, the possibility of novel therapeutic strategies based on drugs that specifically target receptor complexes has been explored [48–52].

In this context, a neuropathological process of significant interest is represented by excitotoxicity, a phenomenon describing the toxic actions of excitatory neurotransmitters (first glutamate) where the prolonged or excessive activation of glutamate receptors triggers a cascade of neurotoxic events leading to loss of neuronal function and cell death [53, 54]. A large body of evidence indicates that excitotoxicity represents a central mechanism in the pathogenesis of many diseases of the CNS [54].

In the present review article, we recapitulate mechanisms underlying excitotoxic processes, with a particular focus on the receptors involved, in order to explore possible modulatory roles played by RRI in neurons and glial cells.

## Mechanisms involved in excitotoxic processes

The term "excitotoxicity" [55] indicates a complex process impacting on almost all subcellular compartments (namely cytosol, mitochondria, endoplasmic reticulum, and nucleus) and leading to neuronal swelling and death [53, 54]. It is triggered by a significant dysregulation of the glutamatergic system [56], characterized by a sustained overactivation of glutamate receptors, followed by a massive influx of cations. Several conditions in the neuron environment may induce excitotoxicity or contribute to its development [54]. They include physical damage of neighboring neurons with release of their glutamate content into the extracellular space [57], oxidative stress [58], oxygen deprivation (as in hypoxic/ischemic states) [59], diseases or disorders that significantly alter the CNS pH [60, 61]. Evidence has also been provided that glucocorticoids can increase neuronal vulnerability to excitotoxicity [62] by impairing energy availability and reducing the production of neurotrophic factors. Their action is mediated by the glucocorticoid receptors (GRs), belonging to a superfamily of nuclear receptors.

Glutamate homeostasis in the neuron environment is mainly controlled by astrocytes, that monitor the extracellular space through a panel of receptors to maintain the balance between their opposing functions of glutamate uptake and release [63]. Impairment of astrocytic glutamate transporters, therefore, makes neurons more susceptible to excitotoxicity. A variety of defense mechanisms, however, can be activated by neurons during excitotoxicity to decrease the damaging effects of the process [54]. Potassium channels, gamma-aminobutyric-acid (GABA) signaling, activation of adenosine $A_1$ receptors, nitric oxide, and expression of heat-shock proteins represent reported examples [64]. Of interest in the framework of the present discussion is the available evidence that estrogens protect neurons against excitotoxic insults [65], an effect mediated by the estrogen receptors. Similar neuroprotective actions have also been documented for other hormones, such as progesterone, testosterone, and neurosteroids [65].

Some more detail on the abovementioned mechanisms and, in particular, on the role played by the receptors involved is the focus of the sections that follow.

### Excitotoxic mechanisms

Glutamatergic dysregulation is the key step leading to excitotoxicity [56]. Glutamate, however, does not directly damage the neurons. Indeed, the excitotoxic cascade is started by a prolonged activation of glutamate receptors [56] resulting in $Na^+$ and $Ca^{2+}$ influx and uptake by mitochondria, which may trigger the production of reactive oxygen species (ROS) and inhibition of ATP production. After glutamate receptor activation both the magnitude and duration of the increase of the intracellular $Ca^{2+}$ concentration are

important determinants of whether neurons degenerate. Indeed, $Ca^{2+}$ concentration values much higher (low micromolar) than the typical cytoplasmic concentration in resting conditions (~100 nM) can be tolerated provided they are transient (seconds to minutes). On the other hand, even a low (~500 nM) increase of cytoplasmic $Ca^{2+}$ concentration can kill the neuron if it is sustained for more than 20–30 min [53]. Glutamate receptors are classified into two main classes [66]: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs).

iGluRs are ligand-gated ion channels permeable to various cations that produce glutamate-evoked excitatory currents, while mGluRs control cellular processes.

Three types of iGluRs have been identified [67], namely *N*-methyl-*D*-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate (KA) receptors, all involved in excitotoxic responses, the NMDA receptors being considered to play the major role due to their high permeability to calcium ions [54]. NMDA receptors are tetrameric structures composed of subunits delineating a central pore and requiring simultaneous binding of glutamate and a co-agonist (*D*-serine or glycine) for activation [68]. Aspartate can also activate NMDA receptors, although with a lower affinity as compared to glutamate [69]. Differences in the type of subunits and in their assembly results in different NMDA receptor subtypes with different functional features (see [54] for a discussion). In this respect, the subtype eNMDA receptor (enriched with GluN2B subunits) has been reported to be particularly involved in activating neurotoxic pathways [70]. AMPA are tetrameric receptors as well, that depending on the subunit composition exhibit different calcium permeability [71]. In particular, AMPA receptors lacking the GluA2 subunit appear to significantly contribute to excitotoxic cell death [72]. As demonstrated by structural biology studies, indeed, when GluA2 is contained within the AMPA receptor the $Ca^{2+}$-permeability is profoundly decreased, due to the presence of arginine at position 607 [73]. A similar property of allowing ion influx following glutamate exposure is also exhibited by KA receptors. They, however, are permeable to sodium and potassium ions and almost impermeable to $Ca^{2+}$ [74]. Furthermore, while AMPA receptors are mostly localized in the postsynaptic membrane, KA receptors are localized both pre- and post-synaptically [75, 76]. Concerning AMPA receptors, an intriguing experimental finding [77] was the observation that rat and mouse cortical neurons secrete exosomes containing two out of the four AMPA subunits which combine to form the receptor tetramer, opening the possibility of an intercellular exchange of elements of the glutamatergic decoding apparatus by microvesicles (the so called “roamer” type of volume transmission [78]) that may represent an interesting mechanism for the modulation of this transmission line.

mGluRs represent a diverse receptor family, including 8 subtypes organized into 3 groups [79]. Group 1 mGluRs ($mGluR_1$ and $mGluR_5$) are coupled to $G_q$ protein. When activated, they stimulate inositol triphosphate production and the release of $Ca^{2+}$ from neuronal stores, contributing to the excitotoxic process [80, 81]. On the contrary, the action of group 2 (subtypes 2 and 3) and group 3 (subtypes 4, 6, 7, and 8) mGluRs was reported to decrease NMDA receptor activity and the risk of excitotoxicity [82]. The effect appeared mediated by a regulation of voltage-gated $K^+$ channels to induce hyperpolarization of the cell, thus reducing the opening probability of the NMDA receptors [82].

An interesting process contributing to excitotoxicity, but not related to glutamate receptors, is the sustained elevation of glucocorticoids [83]. Glucocorticoid hormones are essential for the adaptive response to stress and an important target organ is the brain [84], where the action of corticosteroids is mediated by the high-affinity mineralocorticoid receptor (MR) and the lower affinity GR. They are members of the nuclear receptor superfamily of ligand-dependent transcription factors [85]. In the absence of hormone, GR resides predominantly in the cytoplasm of cells as part of a large multi-protein complex [85]. Upon binding, GR undergoes a conformational change resulting in the dissociation of the associated proteins. This structural rearrangement allows the translocation of GR into the nucleus, where GR binds directly to target DNA sequences called glucocorticoid-responsive elements (GREs) and regulates the expression of target genes [85]. Measurements of intracellular calcium levels in hippocampal neurons exposed to glutamate and other excitatory amino acids have shown that glucocorticoids disrupt cellular calcium homeostasis and promote calcium overload [86]. The suppression of the production of

neurotrophic factors and the suppression of antioxidant defense mechanisms represent other possible endangering mechanisms mediated by glucocorticoids [53]. A rapid effect of glucocorticoids on synaptic glutamate currents has also been recorded in the periventricular nucleus of the hypothalamus mediated by the endocannabinoids [87]. The rapid effects observed, however, were too fast to invoke a genomic mechanism. Thus, the possible involvement of membrane-associated GRs has been suggested [88]. In this respect, several lines of evidence are presently available supporting this glucocorticoid signaling mechanism in the brain [89, 90]. Opioid peptides are another class of stress-related hormones that can affect the excitotoxic process [53]. Dynorphin and nociceptin, for instance, can exacerbate excitotoxicity [91].

## Excitoprotective mechanisms

Neurons may implement a variety of mechanisms protecting against neuronal excitoxicity [54]. During action potentials, for instance, potassium channels can significantly limit neuronal excitability. A first example is provided by small-conductance calcium-dependent potassium channels [92]. Being quite sensitive to transient increases of cytosolic calcium [93] they generate a protective, hyperpolarizing signal [92, 94]. The ATP-dependent potassium channels represent a second important class of potassium channels triggering a protective mechanism. Their conductance, indeed, is enhanced by the ATP depletion that follows excitotoxic insults [95] and their activation at presynaptic sites was shown to inhibits glutamate release [96]. Further neuronal responses to cell stress include those activated by neurotrophic factors (such as BDNF) or by transcription factors (e.g., NF-κB and CREB) [53], and the expression of heat-shock proteins [97].

In the context of the present discussion, however, three more mechanisms deserve particular consideration. The first is the production of adenosine following a neural insult [98]. Adenosine, indeed, inhibits excitatory synaptic transmission, mostly through a presynaptic inhibition of glutamate release, an effect mediated by adenosine $A_1$ receptors. In parallel, the activation of these GPCRs also modulates calcium and potassium channels at the postsynaptic level, leading to a decrease of calcium currents in response to glutamate. The second defensive mechanism involves the inhibitory neurotransmitter GABA that can decrease neural excitability by increasing $Cl^-$ influx through $GABA_A$ receptors [99]. In conditions of sustained excitation, an additional fast-acting neuroprotective mechanism has also been identified, based on the innate capacity of neurons to quench excitation by recruiting $GABA_B$ receptors [100]. Finally, of interest in the present context is emerging research demonstrating the importance of steroid hormones in the regulation of glutamatergic neurotransmission (see [65] for a specific review). The co-localization of AMPA and mGluRs with androgen or estrogen receptors in septum, amygdala, and hypothalamus of rats has been assessed by immunohistochemistry [101], and functional studies indicated a neuroprotective role played by these hormones in ischemic conditions [102]. The effect appears mediated by their receptors, as indicated by studies on estrogen receptors α and β ($ER_\alpha$ and $ER_\beta$), showing that specific agonists of these nuclear receptors can protect hippocampal CA1 neurons during ischemia (where glutamate levels are known to be elevated) [103]. In this context, the modulating effects of progesterone, testosterone, and neurosteroids on glutamatergic neurotransmission also deserve consideration [65]. Although more specific studies on this topic would be needed, available data suggest a neuroprotective role for these hormones as well.

## Glial cells and excitotoxicity

In addition to the well-known metabolic support given to neurons [53, 54], a key function of astrocytes in the CNS is the regulation of neurotransmitter homeostasis [104], as they can uptake synaptically released neurotransmitters, metabolize them, and release back to neurons precursors of those neurotransmitters as well as regulatory gliotransmitters. Extracellular concentrations of GABA, for instance, are under control of GABA transporters (GAT) expressed by both neurons and astrocytes. Astrocytes mainly express GAT-1 and GAT-3 subtypes and it has been estimated that about 20% of extracellular GABA is taken up by these cells [105].

Glutamatergic transmission, however, is in a special way regulated by astrocytes (see [63, 106] for specific reviews on the topic). Glutamatergic synaptic activity generates increases, that can exceed micromolar levels, of glutamate concentration in the extra synaptic space [107]. Although many CNS cells contribute to glutamate removal, astrocytes represent the most efficient elements, being responsible for about 90% of glutamate clearance [108]. The main mechanism of glutamate uptake by astrocytes is represented by two types of glutamate transporters ($Na^+$-dependent and $Na^+$-independent) [63]. High-affinity sodium-dependent glutamate transporters, also known as excitatory amino acid transporters (EAATs), play a major role in the removal of extracellular glutamate by astrocytes and in preventing excitotoxicity [54]. Once taken-up by astrocytes, glutamate can be amidated to glutamine, which is released to the adjacent neurons, where it is converted to glutamate (or GABA) and repackaged into vesicles for release [109]. This astrocytic glutamate-glutamine cycle [63, 110], therefore, is also involved in the maintenance of glutamate homeostasis by sustaining the synthesis of the neurotransmitter [54].

Astrocytes monitor glutamate in their environment by expressing a panel of glutamate receptors [104, 111, 112]. In these cells, the response to glutamatergic signaling is mainly mediated by mGluRs, with $mGluR_1$, $mGluR_3$, and $mGluR_5$ being the most expressed [104, 111]. According to several lines of evidence [104], type 5 mGluR appears as the most relevant, mediating the response of astrocytes to glutamate in many brain areas, such as hippocampus, nucleus accumbens, and thalamus. Ionotropic receptors of the AMPA and NMDA types have also been identified in astrocytes [112, 113]. When compared to neuronal NMDA receptors, astrocytic NMDA receptors appear to exhibit some distinctive features. They, indeed, contain GluN3A receptor subunit, which lowers $Ca^{2+}$ permeability [114], making astrocytes less vulnerable to glutamate-mediated excitotoxicity [113]. Moreover, astrocytic NMDA receptors lack $Mg^{2+}$ block and can be activated without antecedent depolarization [115]. Glutamate receptors also play a role in modulating the activity of glutamate transporters, since group 2 mGluRs can enhance their expression, while group 1 mGluRs and iGluRs downregulate EAATs [63].

The uptake of glutamate into astrocytes can be increased by exogenously administered estradiol, the predominant estrogen in terms of activity [116]. More generally, EAATs may be affected by steroid hormones [65]. The expression of GLT-1 and EAAT3 is upregulated following ischemia, and mRNA and protein levels of these transporters resulted further increased by progesterone and estrogens as compared to ischemia alone [117]. On the contrary, glutamate uptake by astrocytes can be inhibited by adenosine signaling through the adenosine $A_{2A}$ receptors, which are also expressed by astrocytes, due to a physical association of $A_{2A}$ with $Na^+/K^+$-ATPases [118].

In addition to uptake, however, many studies indicate that astrocytes can also release glutamate to the adjacent neurons [119], and a notable subpopulation of astrocytes, selectively expressing synaptic-like glutamate-release machinery, has also been identified in defined anatomical locations [120]. Acting as a gliotransmitter [121], glutamate helps to synchronize neuron firing and modulate the excitatory or inhibitory neuronal transmission [63]. In this respect, the possible impact on synaptic transmission of a significantly increased glutamate release by astrocytes is hardly predictable [122]. Extra synaptic mGluRs should be mainly reached. If astroglial glutamate mainly involves the inhibitory $mGluR_{2\text{-}4}$ ($G_{i/o}$ coupled) located on the nerve terminals, a reduction of neuronal glutamate release would take place with inhibition of glutamate transmission [123] and reduced toxicity. However, if also extra synaptic and postsynaptic $mGluR_1$ and $mGluR_5$ ($G_q$ coupled) are significantly activated by astroglial glutamate, an increase of glutamate synaptic strength may occur, leading to increased intracellular calcium levels [122]. Extracellular signals can modulate astrocytic glutamate release. An example is dopamine, that acting on the $D_2$ receptors expressed by astrocytes inhibits the release of glutamate by these cells [35]. In the context of the present discussion, of interest are data showing that, in addition to glutamate, astrocytes can release *D*-serine (essential for NMDA receptors function), but also ATP, GABA [124], lactate [125], and citrate, chelating zinc ions inhibits NMDA receptor [126].

This dual function of astrocytes, with a balance between opposing actions of glutamate removal and release, confirms the complex role played by these cells in conditions potentially leading to excitotoxic processes [63, 113].

Another glial cell type involved in excitotoxicity is microglia, the resident immune system of the CNS. They are plastic cells, exhibiting a variety of cell morphologies and cell surface markers. They are activated by molecules from damaged neurons and, like peripheral macrophages, they are usually described as characterized by two activation states [127]. In the classical M1 phenotype microglia are cells producing proinflammatory factors. By contrast, in the M2 phenotype, they contribute to neuroprotection and injury repair. A recently characterized process of endocytosis of full-length tau protein by microglial cells [128, 129], triggered by the purinergic G protein-coupled receptor 12 ($P2Y_{12}$), provides an example of protective action in Alzheimer's disease. Increasing evidence, however, suggests that this M1/M2 dichotomy is over-simplified (see [130, 131] for detailed discussions of the topic). Different sub-types of M2-like microglia, indeed, have been identified, and simultaneous expression of classical M1 and M2 markers within individual microglial cells has been reported [132]. These findings indicate that individual microglial cells may be able to adopt complex phenotypes that exhibit both inflammatory and restorative functions. To detect molecular patterns associated with tissue damage, microglial cells exploit a large set of receptors, including all the glutamate receptor types except $mGlu_7$ [131, 133]. Ionotropic [133, 134] and group I/II metabotropic [135] glutamate receptor activation is in general associated with the secretion of cytotoxic or inflammatory factors. Conversely, group III [131, 136] metabotropic receptors were reported to mainly trigger protective actions. Upon specific activation, microglia can also release glutamate, contributing to excitotoxicity.

A schematic view of the main mechanisms is provided in Figure 1, and examples of excitotoxic mechanisms contributing to acute and degenerative CNS diseases are reported in Table 2.

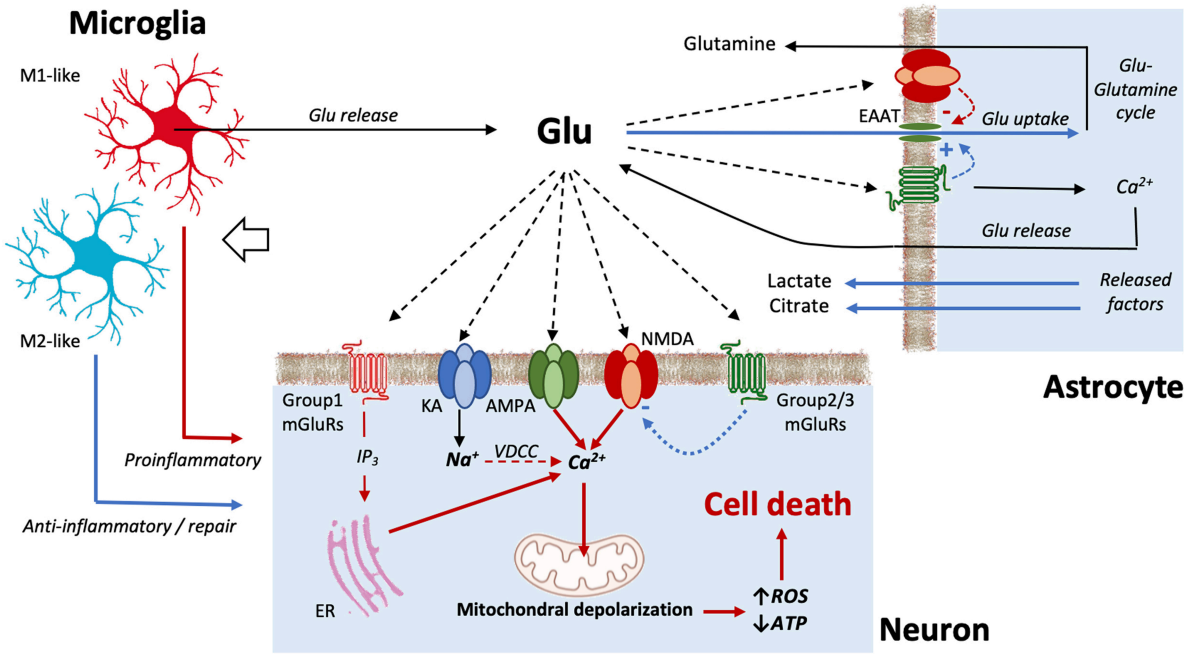


**Figure 1.** Schematic view of the main processes involved in excitotoxicity. Red lines represent processes favoring excitotoxicity; blue lines represent protective processes. In neurons [53, 54], the binding of kainate (KA) receptors results in $Na^+$ influx and membrane depolarization, leading to the opening of voltage-dependent $Ca^{2+}$ channels (VDCC). Further calcium influx is associated to the activation of some forms of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and most importantly of *N*-methyl-*D*-aspartate (NMDA) receptors. The activation of group 1 metabotropic glutamate receptors (mGluRs) also contributes to increase intracellular $Ca^{2+}$ by mobilizing intracellular calcium stores. The resulting increase in cytoplasmic calcium levels may induce $Ca^{2+}$ uptake into the mitochondria that, when excessive, leads to the production of reactive oxygen species (ROS) and inhibits ATP production followed by cell damage or death. The action of activated group 2/3 mGluRs, however, can decrease NMDA receptor activation and protect to some extent the cell. Concerning astrocytes [54, 63], the release of protective factors and, most importantly, their activity of glutamate uptake through excitatory amino acid transporters (EAATs) channels, represent important processes to prevent excitotoxicity. Astrocytes, however, can also release glutamate. Microglial cells monitor the extracellular environment by a large panel of receptors. Depending on the phenotype they assume when activated, microglial cells can trigger pro-inflammatory actions and release of glutamate, or neuroprotective processes [130]

**Table 2.** Excitotoxic processes contributing to diseases of the central nervous system (CNS)

| Disease | Excitotoxic process | References |
|---|---|---|
| Ischemia | • Interruption of blood flow leading to energy failure | [137, 138] |
| | • Impairment of glutamate transport and NMDA receptors overactivation | |
| | • Sustained $Ca^{2+}$ influx | |
| Epilepsy | • Dysregulation of EAATs and increase in extracellular Glu levels | [139, 140] |
| Alzheimer's disease | • Amyloid-$\beta_{1-42}$ oligomers action on eNMDA receptors, leading to sustained $Ca^{2+}$ influx, and mitochondrial and synaptic disfunction | [141, 142] |
| | • Metabolic astrocytic dysfunction and inhibition of lactate production | [143, 144] |
| Amyotrophic lateral sclerosis | • Upregulation of AMPA receptors | [145, 146] |
| | • Interneuron alterations and excitation-inhibition imbalance | |
| | • Downregulation of EAAT2 in astrocytes and altered astrocyte metabolism with release of toxic factors | |
| Parkinson's disease | • Loss of dopamine leading to dysregulation of $Ca^{2+}$ homeostasis | [147, 148] |
| | • Overexpression of $mGluR_5$ receptors | |
| Huntington's disease | • Interaction between mutated HTT protein and the PSD-95 scaffold protein, leading to alteration of the Glu receptors and to impairment of glutamate signaling | [149] |

NMDA: *N*-methyl-*D*-aspartate; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAATs: excitatory amino acid transporters

## Possible modulation of excitotoxic mechanisms by receptor-receptor interactions

In the last decades several lines of evidence demonstrated that almost all the above-mentioned receptors involved in the regulation of excitotoxicity mechanisms may establish structural, allosteric, RRI in neurons, astrocytes, and microglia [111]. These findings suggest receptor complexes as a molecular organization potentially relevant for tuning and modulating the cell processes associated with the dysregulation of the glutamatergic signaling. Thus, receptor complexes are of interest as a possible target of new pharmacological strategies for the treatment of neurodegenerative diseases associated with excitotoxic events. Examples of experimentally identified heteromers of potential interest are reported in Table 3 and will be briefly discussed in the sections that follow.

### Neuronal receptor complexes involving glutamate receptors

As Table 3 illustrates, glutamate receptor subtypes were found to participate in the formation of a quite large number of receptor complexes (see [20, 180] for specific reviews).

mGluRs are class C GPCRs and dimerization is mandatory for these receptors to exert their functions. However, in addition to homodimers, this family of glutamate receptors was shown to form a number of heterodimers as well. A first set of heterodimers involves mGluRs of different types (e.g., $mGluR_1$-$mGluR_2$, $mGluR_1$-$mGluR_5$, $mGluR_2$-$mGluR_3$, $mGluR_2$-$mGluR_4$). Molecular details that govern dimerization and activation of these heterodimers have been recently explored by Wang and collaborators [159] by determining cryo-electron microscopy structures of dimers in distinct conformational states. The results showed that in the inactive states the heterodimers may assume distinct conformations at both the extracellular domains and TM domains. Upon activation, in contrast with mGluR homodimers, the heterodimers assume configurations suggesting an asymmetric mode [159, 181] of signal transduction with only one of the subunits coupling to the G protein. The choice of the subunit for G protein activation likely depends on the stability of the initial inactive conformation, highlighting the complexity of the mGluRs signaling mechanism. A second set of identified receptor complexes containing mGluRs involves receptors from a different family, such as adenosine ($A_1$ and $A_{2A}$), dopamine ($D_2$), serotonin ($5HT_{2A}$), and opioid (MOR) receptors [20], suggesting receptor complexes as a relevant molecular organization to tune glutamatergic transmission. In these heterodimers, synergistic interactions may occur. An example is the $mGluR_2$-$5HT_{2A}$ receptor complex where $5HT_{2A}$-dependent phosphorylation of $mGluR_2$ at Ser843 promotes $mGluR_2$ signaling [182]. On the other side, antagonistic interactions were found to characterize some

**Table 3.** Receptor complexes containing receptors involved in excitotoxicity-associated processes

| Cell location | Receptor complex | Observed interaction | References |
|---|---|---|---|
| Neurons | AMPA-IFNγ | Enhanced AMPA signaling | [150] |
| | AMPA-$D_2$ | Reduced AMPA signaling | [151] |
| | NMDA-$D_1$ | Reduced NMDA signaling | [152] |
| | NMDA-$D_2$ | Reduced NMDA signaling | [153] |
| | NMDA-MOR | Enhanced NMDA signaling | [154] |
| | NMDA-$A_{2A}$ | Cross-antagonism | [155] |
| | NMDA-$mGluR_5$ | Dependent on scaffold proteins | [156] |
| | NMDA-$D_1$-$H_3$ | Cross-antagonism | [157] |
| | $mGluR_1$-$mGluR_5$ | Asymmetric | [158] |
| | $mGluR_2$-$mGluR_3$ | Asymmetric | [159] |
| | $mGluR_2$-$mGluR_4$ | Asymmetric | [159] |
| | $mGluR_2$-$mGluR_7$ | Asymmetric | [160] |
| | $mGluR_1$-$A_1$ | Reduced $mGluR_1$ signaling | [161] |
| | $mGluR_2$-$5HT_{2A}$ | Enhanced $mGluR_2$ signaling | [162] |
| | $mGluR_5$-$A_{2A}$ | Synergistic | [163, 164] |
| | $mGluR_5$-$D_2$ | Reduced $D_2$ signaling | [165] |
| | $mGluR_5$-MOR | Delayed MOR desensitization | [166] |
| | $A_{2A}$-$D_2$-$mGluR_5$ | Reduced $D_2$ signaling | [23] |
| | $A_{2A}$-$D_2$ | Antagonistic | [8] |
| | $A_1$-$A_{2A}$ | Reduced $A_1$ affinity | [167] |
| | $GABA_A$-$D_5$ | Synergistic | [168] |
| | $A_{2A}$-GR | Reduced GR activity | [169] |
| | GR-MR | Synergistic | [170] |
| | $ER_α$-$mGluR_1$ | Increased internalization | [171] |
| Astrocytes | $A_{2A}$-$D_2$ | Antagonistic | [172] |
| | $A_1$-$A_{2A}$ | Antagonistic | [105] |
| | $A_1$-$P2Y_1$ | $A_1$ desensitization | [173] |
| | $A_{2A}$-OTR | Antagonistic | [174] |
| | $D_2$-OTR | Synergistic | [175] |
| Microglia | $P2X_4$-$P2X_7$ | Change of signaling pathways | [176] |
| | $CB_1$-$CB_2$ | Antagonistic | [177] |
| | $A_{2A}$-$CB_2$ | Reduced $CB_2$ signaling | [178] |
| | $GPR_{18}$-$CB_2$ | Cross-antagonism | [179] |

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; IFNγ: interferon-γ receptor; $D_1$, $D_2$, $D_5$: type 1, 2, and 5 dopamine receptors; NMDA: *N*-methyl-*D*-aspartate glutamate receptor; MOR: μ-opiod receptor; $A_1$, $A_{2A}$: type 1 and 2A adenosine receptors; mGluR: metabotropic glutamate receptor; $H_3$: type 3 histamine receptor; $5HT_{2A}$: type 2A serotonin receptor; $GABA_A$: type A gamma-aminobutyric-acid receptor; GR: glucocorticoid receptor; MR: mineralocorticoid receptor; $ER_α$: type α estrogen receptor; P2X, P2Y: purinergic ionotropic and G protein-coupled receptors; OTR: oxytocin receptor; $CB_1$, $CB_2$: type 1 and 2 cannabinoid receptors; $GPR_{18}$: G protein-coupled receptor 18

heterodimers containing mGluRs. An example is the $mGluR_1$-$A_1$ receptor complex in cerebellar Purkinje cells. In this heterodimer, the activation of adenosine $A_1$ receptor attenuates $mGluR_1$-mediated neuronal responses to glutamate [161]. In this context, of great interest is also obtained evidence for the existence extrasynaptically around striatal glutamate synapses of $mGluR_5$-$D_2$ heterodimers [165] and of $D_2$-$A_{2A}$-$mGluR_5$ heterotrimers [23]. In these heteromers, the inhibitory action of dopamine $D_2$ receptors on glutamate release is effectively counterbalanced by $mGluR_5$ and adenosine $A_{2A}$ receptors, contributing to enhancement of the neuron excitability [20].

Heterodimers resulting from direct RRI of iGluRs (NMDA, AMPA) with other receptor types have also been identified. Both $D_1$ and $D_2$ dopamine receptors, for instance, may form receptor complexes with the NMDA receptor, and their activation reduces the operation of NMDA channels [152, 153]. In particular, the interaction between dopamine $D_1$ receptor and the GluN1A subunit of NMDA appears associated with a $D_1$-induced protection from excitotoxicity [152]. Opposingly, the interaction in the NMDA-MOR heterodimer is synergistic [154]. In this receptor complex heteromerization occurs by electrostatic interactions between the two C-termini, which dissociate when morphine activates PKC, leading to enhanced calcium currents through the NMDA channels [20]. Cross-antagonism is observed in the NMDA-$A_{2A}$ heterodimer [155] and in the NMDA-$D_1$-$H_3$ heterotrimer [157]. In both receptor complexes, indeed, the exacerbation of NMDA receptor function was reduced by antagonists of the $A_{2A}$ and $H_3$ receptors respectively. Furthermore, in the heterotrimer $H_3$ antagonists were also found to counteract the effect of an overstimulation of the $D_1$ receptor. A more complex reciprocal interaction has been observed in the NMDA-mGluR$_5$ heteromer. Antagonistic interactions, indeed, have been reported [156] with inhibition of the NMDA currents, but synergistic interactions have also been observed [183] and in the hippocampus, both types of actions were noted [20]. An explanation could be the dynamic association of scaffolding proteins to the heteroreceptor complex [184].

A further example of the important role played by proteins interacting with protomers is provided by the AMPA-$D_2$ heterodimer, where $D_2$ agonist regulation of the AMPA receptor-mediated neurotoxicity is made possible by an increased coupling of the intracellular loop 3 of the $D_2$ receptor to NSF (ATPase *N*-ethylmaleimide-sensitive factor) protein [151]. An enhancement of glutamate excitotoxicity, on the contrary, characterizes the AMPA-IFNγ heterodimer [150], a neuron specific calcium-permeable complex whose formation is triggered by IFNγ.

Experimentally assessed molecular models of receptor complexes involving glutamate receptors are shown in Figure 2A.

### Neuronal receptor complexes involving receptors modulating glutamate homeostasis

Glutamate homeostasis and glutamatergic transmission can be regulated by a variety of extracellular signals. A first example is the typical neuromodulator adenosine [98], whose extracellular levels increase under noxious conditions. The high affinity adenosine $A_1$ receptor plays a major role in neuroprotection, mediating a significant inhibitory action on synaptic transmission and neuronal excitability [188]. However, under noxious conditions the low affinity, facilitatory, adenosine $A_{2A}$ receptors are up regulated [98] and may form heteroreceptor complexes with the $A_1$ receptors [167]. The major RRI in the heterodimer appears to be a reduction of $A_1$ affinity by $A_{2A}$ agonists. Thus, at high concentrations of adenosine, able to activate $A_{2A}$ receptors, an increase of glutamate release was found, contributing to enhanced excitation and possible excitotoxicity [122]. This regulation, therefore, inverts the usual inhibitory action of adenosine acting on $A_1$ receptors, with $A_{2A}$ actions surpassing $A_1$-mediated effects.

As demonstrated by studies on cortico-striatal glutamate terminals, adenosine $A_{2A}$ receptors can also form heteromers with dopamine $D_2$ receptors [8, 189]. Being that the $D_2$ receptor is involved in the inhibition of glutamate release, this receptor complex significantly modulates glutamatergic transmission [190]. The $A_{2A}$-$D_2$ heterodimer (Figure 2B) is probably one of the most studied (see [191] for a recent review) and is characterized by reciprocal antagonistic interactions between the protomers. $A_{2A}$ agonists, indeed, lead to a reduction of the affinity of the $D_2$ agonist-binding site [192], while $D_2$ receptor activation inhibits the $A_{2A}$-induced increase in cAMP accumulation [193] and was shown to slow and partially inhibit the binding of $A_{2A}$ agonists to the receptor [194]. Furthermore, new allosteric binding sites were found to emerge following the formation of the receptor complex. Homocysteine, for instance, can bind to the heterodimer without interfering with the RRI between $A_{2A}$ and $D_2$ receptors, acting as an allosteric antagonist of the dopamine $D_2$ receptor and amplifying the effect of $A_{2A}$ agonists [49].

Quite recent interesting findings indicate that adenosine $A_{2A}$ receptor is a major modulator of glucocorticoid signaling [169] as well. As mentioned before, glucocorticoids by acting on their GR receptor can disrupt cellular calcium homeostasis, promote calcium overload, and contribute to the excitotoxic

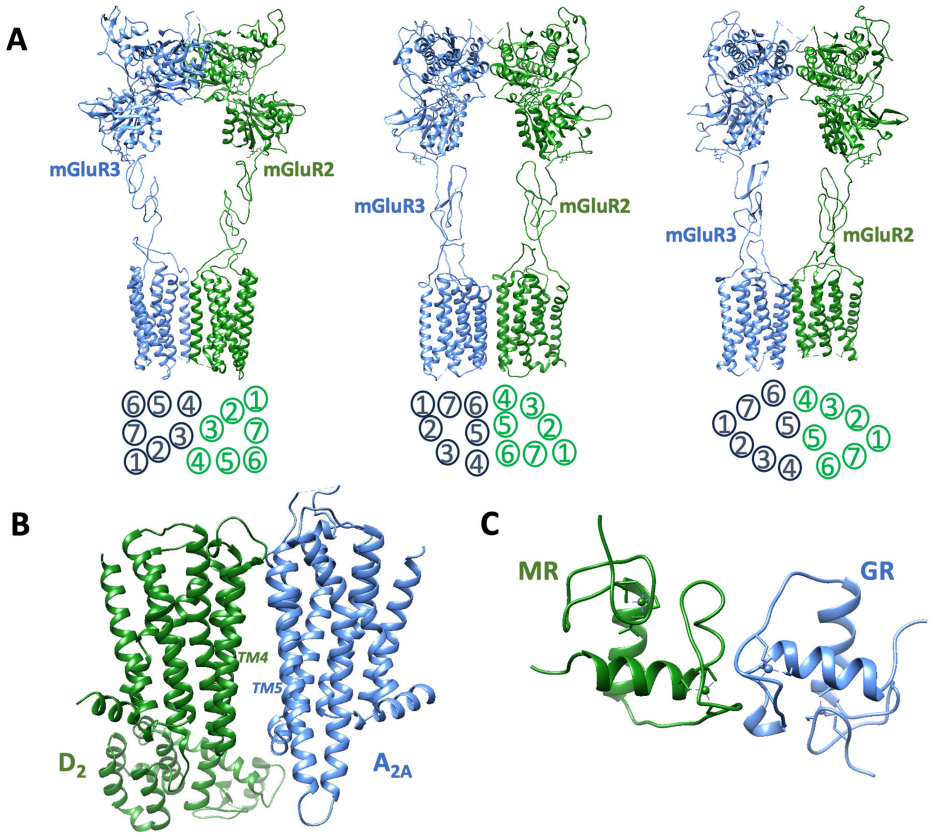


**Figure 2.** Examples of receptor complexes potentially involved in the modulation of excitotoxic processes. (A) Three inactive configurations were exhibited by the metabotropic glutamate receptor 2-3 ($mGluR_2$-$mGluR_3$) heterodimer according to Wang and collaborators [159]. Available data suggest that $mGluR_2$-$mGluR_3$ heterodimers are likely present at mossy fibers terminals in the CA3 region of the hippocampus, a region critically involved in memory processing [185]. Molecular models (Protein Data Bank codes: BJCU, BJCV, BJCZ) are shown. They differ at both the extracellular and transmembrane (TM) domains. The arrangement of TM in the three structures is schematically illustrated below each model. (B) Receptor complex formed by adenosine $A_{2A}$ and dopamine $D_2$ receptors as described by Borroto-Escuela and collaborators [186]. The TM domains forming the interface are indicated. In astrocytes the $A_{2A}$-$D_2$ heterodimer controls the release of glutamate from striatal astrocytic processes and a potential role of this receptor complex in neuropsychiatric disorders has been suggested [45]. (C) Possible structure of the heterodimer between glucocorticoid and mineralocorticoid human receptors, obtained by alignment methods [187] starting from the experimentally assessed structures of the two receptor homodimers (PDB codes: 6BSF and 4TNT). It has been reported that in the hippocampus mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) bind as heterodimers to the same glucocorticoid-responsive element (GRE) sites after an acute stress challenge [170]

process [86]. The possibility of a direct interaction between the membrane $A_{2A}$ receptor and the cytosolic-perimembrane GR has been suggested. It would involve direct RRI between the intracellular domains of $A_{2A}$ and GR, leading to a recruitment of GR and a reduction of its transcriptional activity (see [122] for a discussion). In this context, of substantial interest is a study on the hippocampus [170] showing that acute stress challenges result in an increased interaction of nuclear corticoid receptors GR and MR with their genomic recognition sites. Beyond expectancies, under the analyzed condition they interact with those sites not just as homodimers, but also as heterodimers (Figure 2C). These findings indicate an additional level of complexity in brain glucocorticoid action and may offer suggestions for future research in the almost unexplored field of RRI between nuclear receptors. In this respect, in view of the excitoprotective effects exhibited by steroid hormones (estrogens in particular) [67], of interest is evidence reporting a direct interaction between $ER_\alpha$ and $mGluR_1$ in rats undergoing hormonal treatment [171]. Following treatment with estradiol an increased internalization of both $mGluR_1$ and $ER_\alpha$ was also observed [195]. These findings support the possibility of estrogen/glutamate receptor complexes mediating an interaction between hormonal and glutamatergic signaling.

Concerning GABA transmission, a signaling pathway that can decrease neural excitability [99], heteromerization between $GABA_A$ and dopamine $D_5$ receptors has been demonstrated by Liu and collaborators [168]. The results indicated that the formation of the complex was dependent on the co-activation of the monomers and allowed a reciprocal crosstalk, leading to a reduction in $GABA_A$ signaling and a reduced coupling of $D_5$ to the $G_s$ protein.

## Receptor complexes in astrocytes and microglia

Although less investigated than in neurons, many available data indicate that RRI may play a significant role in astrocytes [111, 196].

Adenosine $A_{2A}$ and dopamine $D_2$ receptors provide the first example. Both receptor types were found to form receptor heteromers in astrocyte processes [172]. From the functional standpoint, the activation of $D_2$ receptors inhibited glutamate release, while the activation of $A_{2A}$ receptors, per se ineffective, abolished the $D_2$-induced release inhibition [197]. Heterodimers between oxytocin receptor (OTR) and $A_{2A}$ or $D_2$ receptors have also been recently identified [174, 175]. Functionally, both receptor complexes appear involved in the regulation of glutamatergic transmission. The interaction between OTR and $D_2$ receptors appears facilitatory, leading to an increase of $D_2$ receptor affinity by oxytocin. Actually, subthreshold concentrations of dopaminergic agonists (too low to activate the astrocytic $D_2$ receptor) become effective in the presence of oxytocin [175]. On the contrary, in the $A_{2A}$-OTR heterodimer the interaction was antagonistic, since the activation of the adenosine receptor abolished the oxytocin-induced inhibition of the release of glutamate by astrocytes [174].

In astrocytes a demonstrated heteromeric association involving the adenosine $A_1$ receptor is with purinergic $P2Y_1$ receptors [173]: As indicated by coimmunoprecipitation methods, these receptors colocalize on astroglial membranes where they organize into receptor complexes. The pharmacological results indicated that within the complex $P2Y_1$ receptor activation induces $A_1$ receptor desensitization. Thus, it has been suggested that this heteromer could play a significant role in the astrocytic modulation of glutamatergic neurotransmission during excitotoxic processes, when large amounts of adenosine and purines are released [173].

Adenosine receptors are also involved in the regulation of GABA uptake, which occurs via the modulation of GATs by the $A_1$ and $A_{2A}$ receptors [196]. By coimmunoprecipitation and BRET assays it has been demonstrated [105] that in astrocytes these receptors can be organized as $A_1$-$A_{2A}$ receptor complexes. Coupled to two different G proteins, $G_s$ and $G_{i/0}$, both regulate GABA transport in an opposite way, with the $A_1$ protomer mediating inhibition of GABA transport and the $A_{2A}$ protomer mediating facilitation of GABA transport into astrocytes. Due to difference in affinity of the two receptor types, at low levels adenosine preferentially binds the $A_1$ protomer, while at high concentrations adenosine activates the $A_{2A}$ protomer. The receptor complex, therefore, was suggested to operate as a dual amplifier to control ambient GABA levels [105].

As briefly illustrated before, some receptor complexes (e.g., $A_{2A}$-$D_2$ and $A_1$-$A_{2A}$) are expressed in both neurons and astrocytes. In this respect, however, it is reasonable to assume [47] that some difference in terms of conformation and interaction of the protomers within the heteromers could occur because of differences (as, for instance, membrane potential [198] and lipid composition [199]) between the two cell types in the membrane microenvironment.

For the present discussion is also of interest the reported RRI between purinergic ionotropic receptors (P2X) (ligand-gated cationic channels) purinergic receptors expressed in microglia and controlling microglia activation [200]. $P2X_4$ and $P2X_7$ are the dominant forms of microglial P2X receptors [133]. Although still a matter of debate [201], the possible occurrence of $P2X_4$-$P2X_7$ heteromers has been reported in these cells [176], probably allowing a more sophisticated regulation of cytokine production and early inflammatory gene expression [133, 176].

As discussed before, microglia can also exert neuroprotective actions. In this respect, there is evidence that endogenous cannabinoids may favor a switch of microglial cells to an anti-inflammatory phenotype [202], and activation of cannabinoid type 2 ($CB_2$) receptor has been proposed to be the mechanism triggering these effects [203]. A number of heteroreceptor complexes involving cannabinoid receptors in microglia have been identified. The first example is the receptor complex $CB_1$-$CB_2$ between the two types of cannabinoid receptors [177], where the activation of one receptor blunts the response of the partner, leading to a wide spectrum of effects when reached by endocannabinoids or by synthetic molecules acting

on cannabinoid receptors [204]. $CB_2$ receptor was also found to form heterodimers with the adenosine $A_{2A}$ receptor [178], and the orphan receptor G protein-coupled receptor 18 ($GPR_{18}$) [179]. In the $A_{2A}$-$CB_2$ receptor complex, the blockade of the $A_{2A}$ receptor leads to increased $CB_2$ signaling, while bidirectional cross-antagonism was observed in the $GPR_{18}$-$CB_2$ heteromer. Thus, both the receptor complexes are of interest from a pharmacological standpoint, since the use of antagonists targeting $A_{2A}$ or $GPR_{18}$ receptors could be useful in the microglia-mediated protection of neuronal death in neurodegenerative diseases [178, 179].

## Conclusions

The term excitotoxicity describes the ability of glutamate, as well as structurally related amino acids, to kill nerve cells, a process that has been proposed to take place not only in acute but also chronic diseases of the CNS [205]. Acute excitotoxic nerve cell death is thought to occur as a consequence of a variety of severe insults including cerebral ischemia, traumatic brain injury, hypoglycemia, and status epilepticus [205] and a body of evidence suggests that exposure of nerve cells to low but above normal concentrations of glutamate (or to a dysregulated glutamatergic transmission) over an extended period of time may also represent a central mechanism in the pathogenesis of many neurodegenerative diseases, including amyotrophic lateral sclerosis and Alzheimer's disease [54].

Excitotoxicity relies on multiple cell mechanisms [53, 54]. Glutamatergic dysregulation, indeed, may occur at the receptor, transporter, or metabolic levels, leading to different types of cellular responses that ultimately culminate in neuronal death. In this respect, several lines of intercellular signaling (such as adenosine, dopamine, opioids, glucocorticoids, and steroid hormones) appear involved in the modulation of the process, acting as factors facilitating or counteracting excitotoxic mechanisms. Of particular interest is also the increasing evidence indicating the complex functional interaction between neurons, astrocytes, and microglia in influencing glutamate homeostasis [105]. The identification of this diversity of mechanisms characterizing and modulating excitotoxicity, together with the understanding that excitotoxicity is a common denominator in many CNS disorders allowed to consider a new perspective on therapy, where the targets are not specific symptoms, but the underlying processes at cell level [54]. In this regard, the quite large number of receptors expressed by both neurons and astrocytes and mediating the effect of the different signals involved in the excitotoxic machinery represent a significant pharmacological target [206].

The evidence reported and discussed in this review supports that most of these receptors can also establish direct allosteric RRI with other receptor proteins, leading to the formation of receptor complexes and allowing a modulation of signal decoding already at the membrane level, which may further expand the spectrum of available strategies. Receptor heteromers, indeed, due to the allosteric interactions between the protomers forming the complex, become endowed with a collective dynamic that significantly influences the chain of events linking ligand recognition to signal transduction [30]. In this respect, pharmacological approaches to target receptor complexes have been explored. The most followed approach has been the well-designed use of agonists/antagonists of a given protomer, since the pharmacology of some agonists/antagonists of a given protomer may show substantial differences among different receptor complexes in terms of affinity and efficacy ([51] provides the example of the $A_{2A}$ antagonist istradefylline, recently approved in the United States as an adjunctive treatment in Parkinson's disease). The development of receptor-complex-specific ligands appears another very promising strategy. Indeed, the possibility to develop bivalent ligands [48] or to exploit allosteric modulators that are selective for structural domains in the heteroreceptor complexes [35, 49] has been demonstrated.

Several aspects, however, remain to be addressed to better understand the possibilities that targeting receptor complexes may offer for the modulation of excitotoxic processes. As a first point, the possibility of RRI and receptor complex formation in receptor families other than GPCRs should be considered. Some data on ion channel receptors [20] and on receptor tyrosine kinases [30] are available, while the field of cytosolic receptors is presently almost unexplored. A second point to emphasize concerns the need for a more detailed mapping of the heteromers of potential interest in order to better understand their

distribution in the brain and to better characterize their location at the cellular level. In this regard, for instance, it should be noted that the research effort to identify and characterize RRI and receptor complexes has been mainly focused on neurons, while available data on astrocytes and microglia are more limited. As briefly discussed here, however, a more intense effort in pharmacological research applied to receptor complexes in glial cells may represent a topic of particular interest in the field of excitotoxic mechanisms, not only to reach a better understanding of the role of neuron-glia crosstalk but also from a therapeutical standpoint. Such a research effort, indeed, may open the possibility of exploring novel, glia-mediated strategies to address neurodegenerative disorders [196].

## Abbreviations

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

CNS: central nervous system

EAATs: excitatory amino acid transporters

GABA: gamma-aminobutyric-acid

GAT: gamma-aminobutyric-acid transporters

GPCRs: G protein-coupled receptors

GRs: glucocorticoid receptors

iGluRs: ionotropic glutamate receptors

KA: kainate

mGluRs: metabotropic glutamate receptors

MR: mineralocorticoid receptor

NMDA: *N*-methyl-*D*-aspartate

P2X: purinergic ionotropic receptors

P2Y: purinergic G protein-coupled receptors

RRI: receptor-receptor interactions

TM: transmembrane

## Declarations

### Author contributions

DG: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. CT, CC, and MM: Investigation. GM and RDC: Writing—review & editing. LFA: Conceptualization, Writing—review & editing. All authors read and approved the submitted version.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

### Consent to publication

Not applicable.

### Availability of data and materials

Not applicable.

### Funding

Not applicable.



## References

1. Prezeau L, Rives ML, Comps-Agrar L, Maurel D, Kniazeff J, Pin JP. Functional crosstalk between GPCRs: with or without oligomerization. Curr Opin Pharmacol. 2010;10:6–13. [DOI] [PubMed]
2. Fuxe K, Agnati LF, Benfenati F, Celani M, Zini I, Zoli M, et al. Evidence for the existence of receptor--receptor interactions in the central nervous system. Studies on the regulation of monoamine receptors by neuropeptides. J Neural Transm Suppl. 1983;18:165–79. [PubMed]
3. Agnati LF, Fuxe K, Zini I, Lenzi P, Hökfelt T. Aspects on receptor regulation and isoreceptor identification. Med Biol. 1980;58:182–7. [PubMed]
4. Agnati LF, Fuxe K, Giardino L, Calza L, Zoli M, Battistini N, et al. Evidence for cholecystokinin-dopamine receptor interactions in the central nervous system of the adult and old rat. Studies on their functional meaning. Ann N Y Acad Sci. 1985;448:315–33. [DOI] [PubMed]
5. Fuxe K, Canals M, Torvinen M, Marcellino D, Terasmaa A, Genedani S, et al. Intramembrane receptor-receptor interactions: a novel principle in molecular medicine. J Neural Transm (Vienna). 2007;114:49–75. [DOI] [PubMed]
6. Kenakin T, Agnati LF, Caron M, Fredholm B, Guidoli D, Kobilka B, et al. International Workshop at the Nobel Forum, Karolinska Institutet on G protein-coupled receptors: finding the words to describe monomers, oligomers, and their molecular mechanisms and defining their meaning. Can a consensus be reached? J Recept Signal Transduct Res. 2010;30:284–6. [DOI] [PubMed]
7. Guidolin D, Tortorella C, Marcoli M, Maura G, Agnati LF. Intercellular Communication in the Central Nervous System as Deduced by Chemical Neuroanatomy and Quantitative Analysis of Images: Impact on Neuropharmacology. Int J Mol Sci. 2022;23:5805. [DOI] [PubMed] [PMC]
8. Trifilieff P, Rives ML, Urizar E, Piskorowski RA, Vishwasrao HD, Castrillon J, et al. Detection of antigen interactions ex vivo by proximity ligation assay: endogenous dopamine D2-adenosine A2A receptor complexes in the striatum. Biotechniques. 2011;51:111–8. [DOI] [PubMed] [PMC]
9. Fernández-Dueñas V, Gómez-Soler M, Valle-León M, Watanabe M, Ferrer I, Ciruela F. Revealing Adenosine $A_{2A}$-Dopamine $D_2$ Receptor Heteromers in Parkinson's Disease Post-Mortem Brain through a New AlphaScreen-Based Assay. Int J Mol Sci. 2019;20:3600. [DOI] [PubMed] [PMC]
10. Petazzi RA, Aji AK, Chiantia S. Fluorescence microscopy methods for the study of protein oligomerization. Prog Mol Biol Transl Sci. 2020;169:1–41. [DOI] [PubMed]
11. De Oliveira PA, Moreno E, Casajuana-Martin N, Casadó-Anguera V, Cai NS, Camacho-Hernandez GA, et al. Preferential Gs protein coupling of the galanin $Gal_1$ receptor in the μ-opioid-$Gal_1$ receptor heterotetramer. Pharmacol Res. 2022;182:106322. [DOI] [PubMed] [PMC]
12. Changeux JP, Christopoulos A. Allosteric modulation as a unifying mechanism for receptor function and regulation. Diabetes Obes Metab. 2017;19:4–21. [DOI] [PubMed]
13. Kenakin T, Miller LJ. Seven transmembrane receptors as shapeshifting proteins: the impact of allosteric modulation and functional selectivity on new drug discovery. Pharmacol Rev. 2010;62:265–304. [DOI] [PubMed] [PMC]
14. Smith NJ, Milligan G. Allostery at G protein-coupled receptor homo- and heteromers: uncharted pharmacological landscapes. Pharmacol Rev. 2010;62:701–25. [DOI] [PubMed] [PMC]

15. Liu J, Nussinov R. Allostery: An Overview of Its History, Concepts, Methods, and Applications. PLoS Comput Biol. 2016;12:e1004966. [DOI] [PubMed] [PMC]
16. Agnati LF, Guidolin D, Leo G, Carone C, Genedani S, Fuxe K. Receptor-receptor interactions: A novel concept in brain integration. Prog Neurobiol. 2010;90:157–75. [DOI] [PubMed]
17. Filizola M, Weinstein H. The study of G-protein coupled receptor oligomerization with computational modeling and bioinformatics. FEBS J. 2005;272:2926–38. [DOI] [PubMed]
18. Simpson LM, Taddese B, Wall ID, Reynolds CA. Bioinformatics and molecular modelling approaches to GPCR oligomerization. Curr Opin Pharmacol. 2010;10:30–7. [DOI] [PubMed]
19. Guidolin D, Ciruela F, Genedani S, Guescini M, Tortorella C, Albertin G, et al. Bioinformatics and mathematical modelling in the study of receptor-receptor interactions and receptor oligomerization: focus on adenosine receptors. Biochim Biophys Acta. 2011;1808:1267–83. [DOI] [PubMed]
20. Borroto-Escuela DO, Tarakanov AO, Brito I, Fuxe K. Glutamate heteroreceptor complexes in the brain. Pharmacol Rep. 2018;70:936–50. [DOI] [PubMed]
21. Carriba P, Navarro G, Ciruela F, Ferré S, Casadó V, Agnati L, et al. Detection of heteromerization of more than two proteins by sequential BRET-FRET. Nat Methods. 2008;5:727–33. [DOI] [PubMed]
22. Pinna A, Bonaventura J, Farré D, Sánchez M, Simola N, Mallol J, et al. L-DOPA disrupts adenosine $A_{2A}$-cannabinoid $CB_1$-dopamine $D_2$ receptor heteromer cross-talk in the striatum of hemiparkinsonian rats: biochemical and behavioral studies. Exp Neurol. 2014;253:180–91. [DOI] [PubMed]
23. Cabello N, Gandía J, Bertarelli DC, Watanabe M, Lluís C, Franco R, et al. Metabotropic glutamate type 5, dopamine $D_2$ and adenosine $A_{2a}$ receptors form higher-order oligomers in living cells. J Neurochem. 2009;109:1497–507. [DOI] [PubMed] [PMC]
24. Beggiato S, Tomasini MC, Borelli AC, Borroto-Escuela DO, Fuxe K, Antonelli T, et al. Functional role of striatal A2A, D2, and mGlu5 receptor interactions in regulating striatopallidal GABA neuronal transmission. J Neurochem. 2016;138:254–64. [DOI] [PubMed]
25. Borroto-Escuela DO, Cuesta-Marti C, Lopez-Salas A, Chruścicka-Smaga B, Crespo-Ramírez M, Tesoro-Cruz E, et al. The oxytocin receptor represents a key hub in the GPCR heteroreceptor network: potential relevance for brain and behavior. Front Mol Neurosci. 2022;15:1055344. [DOI] [PubMed] [PMC]
26. Fuxe K, Agnati LF. Receptor-receptor interactions in the central nervous system. A new integrative mechanism in synapses. Med Res Rev. 1985;5:441–82. [DOI] [PubMed]
27. Zoli M, Guidolin D, Fuxe K, Agnati LF. The receptor mosaic hypothesis of the engram: possible relevance of Boolean network modeling. Int J Neural Syst. 1996;7:363–8. [DOI] [PubMed]
28. Fuxe K, Borroto-Escuela DO, Ciruela F, Guidolin D, Agnati LF. Receptor-receptor interactions in heteroreceptor complexes: a new principle in biology. Focus on their role in learning and memory. Neurosci Discov. 2014;2:6. [DOI]
29. Fuxe K, Borroto-Escuela DO. Volume transmission and receptor-receptor interactions in heteroreceptor complexes: understanding the role of new concepts for brain communication. Neural Regen Res. 2016;11:1220–3. [DOI] [PubMed] [PMC]
30. Guidolin D, Marcoli M, Tortorella C, Maura G, Agnati LF. Receptor-Receptor Interactions as a Widespread Phenomenon: Novel Targets for Drug Development? Front Endocrinol (Lausanne). 2019;10:53. [DOI] [PubMed] [PMC]
31. Fuxe K, Marcellino D, Guidolin D, Woods AS, Agnati L. Brain receptor mosaics and their intramembrane receptor-receptor interactions: molecular integration in transmission and novel targets for drug development. J Acupunct Meridian Stud. 2009;2:1–25. [DOI] [PubMed]
32. Gainetdinov RR, Premont RT, Bohn LM, Lefkowitz RJ, Caron MG. Desensitization of G protein-coupled receptors and neuronal functions. Annu Rev Neurosci. 2004;27:107–44. [DOI] [PubMed]
33. Ferrada C, Moreno E, Casadó V, Bongers G, Cortés A, Mallol J, et al. Marked changes in signal transduction upon heteromerization of dopamine $D_1$ and histamine $H_3$ receptors. Br J Pharmacol. 2009;157:64–75. [DOI] [PubMed] [PMC]

34. Smith JS, Rajagopal S. The β-Arrestins: Multifunctional Regulators of G Protein-coupled Receptors. J Biol Chem. 2016;291:8969–77. [DOI] [PubMed] [PMC]
35. Cervetto C, Venturini A, Guidolin D, Maura G, Passalacqua M, Tacchetti C, et al. Homocysteine and A2A-D2 Receptor-Receptor Interaction at Striatal Astrocyte Processes. J Mol Neurosci. 2018;65: 456–66. [DOI] [PubMed]
36. Romero GG. The Role of the Cell Background in Biased Signaling. In: Arey BJ, editor. Biased Signaling in Physiology, Pharmacology and Therapeutics. San Diego: Academic Press; 2014. pp. 41–79. [DOI]
37. Franco R, Lluis C, Canela EI, Mallol J, Agnati L, Casadó V, et al. Receptor-receptor interactions involving adenosine $A_1$ or dopamine $D_1$ receptors and accessory proteins. J Neural Transm (Vienna). 2007;114:93–104. [DOI] [PubMed]
38. Farran B. An update on the physiological and therapeutic relevance of GPCR oligomers. Pharmacol Res. 2017;117:303–27. [DOI] [PubMed]
39. Borroto-Escuela DO, Carlsson J, Ambrogini P, Narváez M, Wydra K, Tarakanov AO, et al. Understanding the Role of GPCR Heteroreceptor Complexes in Modulating the Brain Networks in Health and Disease. Front Cell Neurosci. 2017;11:37. [DOI] [PubMed] [PMC]
40. Guidolin D, Marcoli M, Maura G, Agnati LF. New dimensions of connectomics and network plasticity in the central nervous system. Rev Neurosci. 2017;28:113–32. [DOI] [PubMed]
41. Kasai RS, Ito SV, Awane RM, Fujiwara TK, Kusumi A. The Class-A GPCR Dopamine D2 Receptor Forms Transient Dimers Stabilized by Agonists: Detection by Single-Molecule Tracking. Cell Biochem Biophys. 2018;76:29–37. [DOI] [PubMed] [PMC]
42. Kleinau G, Müller A, Biebermann H. Oligomerization of GPCRs involved in endocrine regulation. J Mol Endocrinol. 2016;57:R59–80. [DOI] [PubMed]
43. Fuxe K, Marcellino D, Rivera A, Diaz-Cabiale Z, Filip M, Gago B, et al. Receptor-receptor interactions within receptor mosaics. Impact on neuropsychopharmacology. Brain Res Rev. 2008;58:415–52. [DOI] [PubMed]
44. Ferré S, Belcher AM, Bonaventura J, Quiroz C, Sánchez-Soto M, Casadó-Anguera V, et al. Functional and pharmacological role of the dopamine $D_4$ receptor and its polymorphic variants. Front Endocrinol (Lausanne). 2022;13:1014678. [DOI] [PubMed] [PMC]
45. Cervetto C, Maura G, Guidolin D, Amato S, Ceccoli C, Agnati LF, et al. Striatal astrocytic A2A-D2 receptor-receptor interactions and their role in neuropsychiatric disorders. Neuropharmacology. 2023;237:109636. [DOI] [PubMed]
46. Romero-Fernandez W, Carvajal-Tapia C, Prusky A, Katdare KA, Wang E, Shostak A, et al. Detection, visualization and quantification of protein complexes in human Alzheimer's disease brains using proximity ligation assay. Sci Rep. 2023;13:11948. [DOI] [PubMed] [PMC]
47. Guidolin D, Tortorella C, Marcoli M, Cervetto C, De Caro R, Maura G, et al. Modulation of Neuron and Astrocyte Dopamine Receptors via Receptor-Receptor Interactions. Pharmaceuticals (Basel). 2023; 16:1427. [DOI] [PubMed] [PMC]
48. Daniels DJ, Lenard NR, Etienne CL, Law PY, Roerig SC, Portoghese PS. Opioid-induced tolerance and dependence in mice is modulated by the distance between pharmacophores in a bivalent ligand series. Proc Natl Acad Sci U S A. 2005;102:19208–13. [DOI] [PubMed] [PMC]
49. Agnati LF, Ferré S, Genedani S, Leo G, Guidolin D, Filaferro M, et al. Allosteric modulation of dopamine $D_2$ receptors by homocysteine. J Proteome Res. 2006;5:3077–83. [DOI] [PubMed]
50. Jonas KC, Hanyaloglu AC. Impact of G protein-coupled receptor heteromers in endocrine systems. Mol Cell Endocrinol. 2017;449:21–7. [DOI] [PubMed]
51. Chen JF, Cunha RA. The belated US FDA approval of the adenosine $A_{2A}$ receptor antagonist istradefylline for treatment of Parkinson's disease. Purinergic Signal. 2020;16:167–74. [DOI] [PubMed] [PMC]

52. Franco R, Navarro G. Neuroprotection afforded by targeting G protein-coupled receptors in heteromers and by heteromer-selective drugs. Front Pharmacol. 2023;14:1222158. [DOI] [PubMed] [PMC]
53. Mattson MP. Excitotoxicity. In: Fink G, editor. Stress: Physiology, Biochemistry, and Pathology. Cambridge: Academic Press; 2019. pp. 125–34. [DOI]
54. Armada-Moreira A, Gomes JI, Pina CC, Savchak OK, Gonçalves-Ribeiro J, Rei N, et al. Going the Extra (Synaptic) Mile: Excitotoxicity as the Road Toward Neurodegenerative Diseases. Front Cell Neurosci. 2020;14:90. [DOI] [PubMed] [PMC]
55. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. Science. 1969;164:719–21. [DOI] [PubMed]
56. Connolly NM, Prehn JH. The metabolic response to excitotoxicity - lessons from single-cell imaging. J Bioenerg Biomembr. 2015;47:75–88. [DOI] [PubMed]
57. Mehta A, Prabhakar M, Kumar P, Deshmukh R, Sharma PL. Excitotoxicity: bridge to various triggers in neurodegenerative disorders. Eur J Pharmacol. 2013;698:6–18. [DOI] [PubMed]
58. Pellegrini-Giampietro DE, Cherici G, Alesiani M, Carla V, Moroni F. Excitatory amino acid release and free radical formation may cooperate in the genesis of ischemia-induced neuronal damage. J Neurosci. 1990;10:1035–41. [DOI] [PubMed] [PMC]
59. Prentice H, Modi JP, Wu JY. Mechanisms of Neuronal Protection against Excitotoxicity, Endoplasmic Reticulum Stress, and Mitochondrial Dysfunction in Stroke and Neurodegenerative Diseases. Oxid Med Cell Longev. 2015;2015:964518. [DOI] [PubMed] [PMC]
60. Kraig RP, Petito CK, Plum F, Pulsinelli WA. Hydrogen ions kill brain at concentrations reached in ischemia. J Cereb Blood Flow Metab. 1987;7:379–86. [DOI] [PubMed] [PMC]
61. Zhang S, Sun P, Sun Z, Zhang J, Zhou J, Gu Y. Cortical GABAergic neurons are more severely impaired by alkalosis than acidosis. BMC Neurol. 2013;13:192. [DOI] [PubMed] [PMC]
62. Sapolsky RM. Stress, Glucocorticoids, and Damage to the Nervous System: The Current State of Confusion. Stress. 1996;1:1–19. [DOI] [PubMed]
63. Mahmoud S, Gharagozloo M, Simard C, Gris D. Astrocytes Maintain Glutamate Homeostasis in the CNS by Controlling the Balance between Glutamate Uptake and Release. Cells. 2019;8:184. [DOI] [PubMed] [PMC]
64. Sapolsky RM. Cellular defenses against excitotoxic insults. J Neurochem. 2001;76:1601–11. [DOI] [PubMed]
65. Goyette MJ, Murray SL, Saldanha CJ, Holton K. Sex Hormones, Neurosteroids, and Glutamatergic Neurotransmission: A Review of the Literature. Neuroendocrinology. 2023;113:905–14. [DOI] [PubMed]
66. Reiner A, Levitz J. Glutamatergic Signaling in the Central Nervous System: Ionotropic and Metabotropic Receptors in Concert. Neuron. 2018;98:1080–98. [DOI] [PubMed] [PMC]
67. Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia AS, McNamara JO, et al., editors. Neuroscience. 2nd ed. Sunderland: Sinauer Associates; 2001.
68. Guo H, Camargo LM, Yeboah F, Digan ME, Niu H, Pan Y, et al. A NMDA-receptor calcium influx assay sensitive to stimulation by glutamate and glycine/D-serine. Sci Rep. 2017;7:11608. [DOI] [PubMed] [PMC]
69. Chen PE, Geballe MT, Stansfeld PJ, Johnston AR, Yuan H, Jacob AL, et al. Structural features of the glutamate binding site in recombinant NR1/NR2A *N*-methyl-D-aspartate receptors determined by site-directed mutagenesis and molecular modeling. Mol Pharmacol. 2005;67:1470–84. [DOI] [PubMed]
70. Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nat Rev Neurosci. 2010;11:682–96. [DOI] [PubMed] [PMC]
71. Pál B. Involvement of extrasynaptic glutamate in physiological and pathophysiological changes of neuronal excitability. Cell Mol Life Sci. 2018;75:2917–49. [DOI] [PubMed] [PMC]

72. Wright A, Vissel B. The essential role of AMPA receptor GluR2 subunit RNA editing in the normal and diseased brain. Front Mol Neurosci. 2012;5:34. [DOI] [PubMed] [PMC]
73. Hume RI, Dingledine R, Heinemann SF. Identification of a site in glutamate receptor subunits that controls calcium permeability. Science. 1991;253:1028–31. [DOI] [PubMed]
74. Huettner JE. Kainate receptors and synaptic transmission. Prog Neurobiol. 2003;70:387–407. [DOI] [PubMed]
75. Chittajallu R, Vignes M, Dev KK, Barnes JM, Collingridge GL, Henley JM. Regulation of glutamate release by presynaptic kainate receptors in the hippocampus. Nature. 1996;379:78–81. [DOI] [PubMed]
76. Castillo PE, Malenka RC, Nicoll RA. Kainate receptors mediate a slow postsynaptic current in hippocampal CA3 neurons. Nature. 1997;388:182–6. [DOI] [PubMed]
77. Fauré J, Lachenal G, Court M, Hirrlinger J, Chatellard-Causse C, Blot B, et al. Exosomes are released by cultured cortical neurones. Mol Cell Neurosci. 2006;31:642–8. [DOI] [PubMed]
78. Agnati LF, Guidolin D, Guescini M, Genedani S, Fuxe K. Understanding wiring and volume transmission. Brain Res Rev. 2010;64:137–59. [DOI] [PubMed]
79. Niswender CM, Conn PJ. Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol. 2010;50:295–322. [DOI] [PubMed] [PMC]
80. Skeberdis VA, Lan J, Opitz T, Zheng X, Bennett MV, Zukin RS. mGluR1-mediated potentiation of NMDA receptors involves a rise in intracellular calcium and activation of protein kinase C. Neuropharmacology. 2001;40:856–65. [DOI] [PubMed]
81. Lea PM, Custer SJ, Vicini S, Faden AI. Neuronal and glial mGluR5 modulation prevents stretch-induced enhancement of NMDA receptor current. Pharmacol Biochem Behav. 2002;73:287–98. [DOI] [PubMed]
82. Ambrosini A, Bresciani L, Fracchia S, Brunello N, Racagni G. Metabotropic glutamate receptors negatively coupled to adenylate cyclase inhibit *N*-methyl-D-aspartate receptor activity and prevent neurotoxicity in mesencephalic neurons in vitro. Mol Pharmacol. 1995;47:1057–64. [PubMed]
83. McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci. 2004;1032:1–7. [DOI] [PubMed]
84. Koning ACAM, Buurstede JC, van Weert LTCM, Meijer OC. Glucocorticoid and Mineralocorticoid Receptors in the Brain: A Transcriptional Perspective. J Endocr Soc. 2019;3:1917–30. [DOI] [PubMed] [PMC]
85. Oakley RH, Cidlowski JA. The biology of the glucocorticoid receptor: new signaling mechanisms in health and disease. J Allergy Clin Immunol. 2013;132:1033–44. [DOI] [PubMed] [PMC]
86. Xiao X, Zhang H, Wang H, Li Q, Zhang T. Neuroprotective effect of amantadine on corticosterone-induced abnormal glutamatergic synaptic transmission of CA3-CA1 pathway in rat's hippocampal slices. Synapse. 2017;71:e22010. [DOI] [PubMed]
87. Di S, Malcher-Lopes R, Halmos KC, Tasker JG. Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. J Neurosci. 2003;23:4850–7. [DOI] [PubMed] [PMC]
88. Tasker JG, Di S, Malcher-Lopes R. Rapid central corticosteroid effects: evidence for membrane glucocorticoid receptors in the brain. Integr Comp Biol. 2005;45:665–71. [DOI] [PubMed]
89. Herman JP. The neuroendocrinology of stress: Glucocorticoid signaling mechanisms. Psychoneuroendocrinology. 2022;137:105641. [DOI] [PubMed]
90. Wang Y, Zhang Y, Hu J, Pan C, Gao Y, Liu Q, et al. Glucocorticoids modulate neural activity via a rapid non-genomic effect on Kv2.2 channels in the central nervous system. Neurobiol Stress. 2023;28:100593. [DOI] [PubMed] [PMC]

91. Laudenbach V, Calo G, Guerrini R, Lamboley G, Benoist JF, Evrard P, et al. Nociceptin/orphanin FQ exacerbates excitotoxic white-matter lesions in the murine neonatal brain. J Clin Invest. 2001;107: 457–66. [DOI] [PubMed] [PMC]
92. Sah P. $Ca^{2+}$-activated $K^+$ currents in neurones: types, physiological roles and modulation. Trends Neurosci. 1996;19:150–4. [DOI] [PubMed]
93. Blatz AL, Magleby KL. Calcium-activated potassium channels. Trends Neurosci. 1987;10:463–7. [DOI]
94. Honrath B, Krabbendam IE, Culmsee C, Dolga AM. Small conductance $Ca^{2+}$-activated $K^+$ channels in the plasma membrane, mitochondria and the ER: Pharmacology and implications in neuronal diseases. Neurochem Int. 2017;109:13–23. [DOI] [PubMed]
95. Trapp S, Ballanyi K. KATP channel mediation of anoxia-induced outward current in rat dorsal vagal neurons in vitro. J Physiol. 1995;487:37–50. [DOI] [PubMed] [PMC]
96. Bancila V, Nikonenko I, Dunant Y, Bloc A. Zinc inhibits glutamate release via activation of pre-synaptic K channels and reduces ischaemic damage in rat hippocampus. J Neurochem. 2004;90: 1243–50. [DOI] [PubMed]
97. Yenari MA, Giffard RG, Sapolsky RM, Steinberg GK. The neuroprotective potential of heat shock protein 70 (HSP70). Mol Med Today. 1999;5:525–31. [DOI] [PubMed]
98. Cunha RA. Neuroprotection by adenosine in the brain: From $A_1$ receptor activation to $A_{2A}$ receptor blockade. Purinergic Signal. 2005;1:111–34. [DOI] [PubMed] [PMC]
99. Winkler P, Luhmann HJ, Kilb W. Taurine potentiates the anticonvulsive effect of the $GABA_A$ agonist muscimol and pentobarbital in the immature mouse hippocampus. Epilepsia. 2019;60:464–74. [DOI] [PubMed]
100. Samson AJ, Robertson G, Zagnoni M, Connolly CN. Neuronal networks provide rapid neuroprotection against spreading toxicity. Sci Rep. 2016;6:33746. [DOI] [PubMed] [PMC]
101. Diano S, Naftolin F, Horvath TL. Gonadal steroids target AMPA glutamate receptor-containing neurons in the rat hypothalamus, septum and amygdala: a morphological and biochemical study. Endocrinology. 1997;138:778–89. [DOI] [PubMed]
102. Gulinello M, Lebesgue D, Jover-Mengual T, Zukin RS, Etgen AM. Acute and chronic estradiol treatments reduce memory deficits induced by transient global ischemia in female rats. Horm Behav. 2006;49:246–60. [DOI] [PubMed] [PMC]
103. Miller NR, Jover T, Cohen HW, Zukin RS, Etgen AM. Estrogen can act via estrogen receptor alpha and beta to protect hippocampal neurons against global ischemia-induced cell death. Endocrinology. 2005;146:3070–9. [DOI] [PubMed]
104. Kofuji P, Araque A. G-Protein-Coupled Receptors in Astrocyte-Neuron Communication. Neuroscience. 2021;456:71–84. [DOI] [PubMed] [PMC]
105. Cristóvão-Ferreira S, Navarro G, Brugarolas M, Pérez-Capote K, Vaz SH, Fattorini G, et al. $A_1R$-$A_{2A}R$ heteromers coupled to $G_s$ and $G_{i/0}$ proteins modulate GABA transport into astrocytes. Purinergic Signal. 2013;9:433–49. [DOI] [PubMed] [PMC]
106. Cuellar-Santoyo AO, Ruiz-Rodríguez VM, Mares-Barbosa TB, Patrón-Soberano A, Howe AG, Portales-Pérez DP, et al. Revealing the contribution of astrocytes to glutamatergic neuronal transmission. Front Cell Neurosci. 2023;16:1037641. [DOI] [PubMed] [PMC]
107. Okubo Y, Sekiya H, Namiki S, Sakamoto H, Iinuma S, Yamasaki M, et al. Imaging extrasynaptic glutamate dynamics in the brain. Proc Natl Acad Sci U S A. 2010;107:6526–31. [DOI] [PubMed] [PMC]
108. Eulenburg V, Gomeza J. Neurotransmitter transporters expressed in glial cells as regulators of synapse function. Brain Res Rev. 2010;63:103–12. [DOI] [PubMed]
109. Rodríguez-Arellano JJ, Parpura V, Zorec R, Verkhratsky A. Astrocytes in physiological aging and Alzheimer's disease. Neuroscience. 2016;323:170–82. [DOI] [PubMed]
110. Waniewski RA, Martin DL. Exogenous glutamate is metabolized to glutamine and exported by rat primary astrocyte cultures. J Neurochem. 1986;47:304–13. [DOI] [PubMed]

111. Guidolin D, Tortorella C, Marcoli M, Cervetto C, Maura G, Agnati LF. Receptor-receptor interactions and microvesicle exchange as mechanisms modulating signaling between neurons and astrocytes. Neuropharmacology. 2023;231:109509. [DOI] [PubMed]
112. Fan D, Grooms SY, Araneda RC, Johnson AB, Dobrenis K, Kessler JA, et al. AMPA receptor protein expression and function in astrocytes cultured from hippocampus. J Neurosci Res. 1999;57:557–71. [PubMed]
113. Belov Kirdajova D, Kriska J, Tureckova J, Anderova M. Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells. Front Cell Neurosci. 2020;14:51. [DOI] [PubMed] [PMC]
114. Palygin O, Lalo U, Pankratov Y. Distinct pharmacological and functional properties of NMDA receptors in mouse cortical astrocytes. Br J Pharmacol. 2011;163:1755–66. [DOI] [PubMed] [PMC]
115. Lalo U, Pankratov Y, Kirchhoff F, North RA, Verkhratsky A. NMDA receptors mediate neuron-to-glia signaling in mouse cortical astrocytes. J Neurosci. 2006;26:2673–83. [DOI] [PubMed] [PMC]
116. Liang Z, Valla J, Sefidvash-Hockley S, Rogers J, Li R. Effects of estrogen treatment on glutamate uptake in cultured human astrocytes derived from cortex of Alzheimer's disease patients. J Neurochem. 2002;80:807–14. [DOI] [PubMed]
117. Nematipour S, Vahidinia Z, Nejati M, Naderian H, Beyer C, Azami Tameh A. Estrogen and progesterone attenuate glutamate neurotoxicity via regulation of EAAT3 and GLT-1 in a rat model of ischemic stroke. Iran J Basic Med Sci. 2020;23:1346–52. [DOI] [PubMed] [PMC]
118. Matos M, Augusto E, Agostinho P, Cunha RA, Chen JF. Antagonistic interaction between adenosine $A_{2A}$ receptors and $Na^+/K^+$-ATPase-α2 controlling glutamate uptake in astrocytes. J Neurosci. 2013;33:18492–502. [DOI] [PubMed] [PMC]
119. Malarkey EB, Parpura V. Mechanisms of glutamate release from astrocytes. Neurochem Int. 2008;52:142–54. [DOI] [PubMed] [PMC]
120. de Ceglia R, Ledonne A, Litvin DG, Lind BL, Carriero G, Latagliata EC, et al. Specialized astrocytes mediate glutamatergic gliotransmission in the CNS. Nature. 2023;622:120–9. [DOI] [PubMed] [PMC]
121. Harada K, Kamiya T, Tsuboi T. Gliotransmitter Release from Astrocytes: Functional, Developmental, and Pathological Implications in the Brain. Front Neurosci. 2016;9:499. [DOI] [PubMed] [PMC]
122. Borroto-Escuela DO, Hinz S, Navarro G, Franco R, Müller CE, Fuxe K. Understanding the Role of Adenosine A2AR Heteroreceptor Complexes in Neurodegeneration and Neuroinflammation. Front Neurosci. 2018;12:43. [DOI] [PubMed] [PMC]
123. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci. 2009;10:561–72. [DOI] [PubMed]
124. Lee S, Yoon BE, Berglund K, Oh SJ, Park H, Shin HS, et al. Channel-mediated tonic GABA release from glia. Science. 2010;330:790–6. [DOI] [PubMed]
125. Mason S. Lactate Shuttles in Neuroenergetics-Homeostasis, Allostasis and Beyond. Front Neurosci. 2017;11:43. [DOI] [PubMed] [PMC]
126. Schousboe A, Westergaard N, Waagepetersen HS, Larsson OM, Bakken IJ, Sonnewald U. Trafficking between glia and neurons of TCA cycle intermediates and related metabolites. Glia. 1997;21:99–105. [PubMed]
127. Eggen BJL, Raj D, Hanisch UK, Boddeke HW. Microglial phenotype and adaptation. J Neuroimmune Pharmacol. 2013;8:807–23. [DOI] [PubMed]
128. Maeda J, Minamihisamatsu T, Shimojo M, Zhou X, Ono M, Matsuba Y, et al. Distinct microglial response against Alzheimer's amyloid and tau pathologies characterized by P2Y12 receptor. Brain Commun. 2021;3:fcab011. [DOI] [PubMed] [PMC]
129. Chidambaram H, Das R, Chinnathambi S. G-protein coupled purinergic P2Y12 receptor interacts and internalizes $Tau^{RD}$-mediated by membrane-associated actin cytoskeleton remodeling in microglia. Eur J Cell Biol. 2022;101:151201. [DOI] [PubMed]
130. Franco R, Fernández-Suárez D. Alternatively activated microglia and macrophages in the central nervous system. Prog Neurobiol. 2015;131:65–86. [DOI] [PubMed]

131. Zhang X, Wang D, Zhang B, Zhu J, Zhou Z, Cui L. Regulation of microglia by glutamate and its signal pathway in neurodegenerative diseases. Drug Discov Today. 2020;25:1074–85. [DOI] [PubMed]
132. Kim CC, Nakamura MC, Hsieh CL. Brain trauma elicits non-canonical macrophage activation states. J Neuroinflammation. 2016;13:117. [DOI] [PubMed] [PMC]
133. Domercq M, Vázquez-Villoldo N, Matute C. Neurotransmitter signaling in the pathophysiology of microglia. Front Cell Neurosci. 2013;7:49. [DOI] [PubMed] [PMC]
134. Kaindl AM, Degos V, Peineau S, Gouadon E, Chhor V, Loron G, et al. Activation of microglial *N*-methyl-D-aspartate receptors triggers inflammation and neuronal cell death in the developing and mature brain. Ann Neurol. 2012;72:536–49. [DOI] [PubMed]
135. Kumar A, Dhull DK, Mishra PS. Therapeutic potential of mGluR5 targeting in Alzheimer's disease. Front Neurosci. 2015;9:215. [DOI] [PubMed] [PMC]
136. Taylor DL, Diemel LT, Pocock JM. Activation of microglial group III metabotropic glutamate receptors protects neurons against microglial neurotoxicity. J Neurosci. 2003;23:2150–60. [DOI] [PubMed] [PMC]
137. Lai TW, Zhang S, Wang YT. Excitotoxicity and stroke: identifying novel targets for neuroprotection. Prog Neurobiol. 2014;115:157–88. [DOI] [PubMed]
138. O'Donovan SM, Sullivan CR, McCullumsmith RE. The role of glutamate transporters in the pathophysiology of neuropsychiatric disorders. NPJ Schizophr. 2017;3:32. [DOI] [PubMed] [PMC]
139. Albrecht J, Zielińska M. Mechanisms of Excessive Extracellular Glutamate Accumulation in Temporal Lobe Epilepsy. Neurochem Res. 2017;42:1724–34. [DOI] [PubMed]
140. Peterson AR, Binder DK. Regulation of Synaptosomal GLT-1 and GLAST during Epileptogenesis. Neuroscience. 2019;411:185–201. [DOI] [PubMed]
141. Li S, Jin M, Koeglsperger T, Shepardson NE, Shankar GM, Selkoe DJ. Soluble Aβ oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. J Neurosci. 2011;31:6627–38. [DOI] [PubMed] [PMC]
142. Texidó L, Martín-Satué M, Alberdi E, Solsona C, Matute C. Amyloid β peptide oligomers directly activate NMDA receptors. Cell Calcium. 2011;49:184–90. [DOI] [PubMed]
143. Angelova PR, Abramov AY. Interaction of neurons and astrocytes underlies the mechanism of Aβ-induced neurotoxicity. Biochem Soc Trans. 2014;42:1286–90. [DOI] [PubMed]
144. Dienel GA. The metabolic trinity, glucose-glycogen-lactate, links astrocytes and neurons in brain energetics, signaling, memory, and gene expression. Neurosci Lett. 2017;637:18–25. [DOI] [PubMed]
145. Arnold FJ, Putka AF, Raychaudhuri U, Hsu S, Bedlack RS, Bennett CL, et al. Revisiting Glutamate Excitotoxicity in Amyotrophic Lateral Sclerosis and Age-Related Neurodegeneration. Int J Mol Sci. 2024;25:5587. [DOI] [PubMed] [PMC]
146. Bae JS, Simon NG, Menon P, Vucic S, Kiernan MC. The puzzling case of hyperexcitability in amyotrophic lateral sclerosis. J Clin Neurol. 2013;9:65–74. [DOI] [PubMed] [PMC]
147. Glaser T, Silva JB, Juvenal GA, Maiolini PN, Turrini N, Petiz LL, et al. Various facets of excitotoxicity. Explor Neuroprot Ther. 2022;2:36–64. [DOI]
148. Price DL, Rockenstein E, Ubhi K, Phung V, MacLean-Lewis N, Askay D, et al. Alterations in mGluR5 expression and signaling in Lewy body disease and in transgenic models of alpha-synucleinopathy--implications for excitotoxicity. PLoS One. 2010;5:e14020. [DOI] [PubMed] [PMC]
149. Fan J, Cowan CM, Zhang LY, Hayden MR, Raymond LA. Interaction of postsynaptic density protein-95 with NMDA receptors influences excitotoxicity in the yeast artificial chromosome mouse model of Huntington's disease. J Neurosci. 2009;29:10928–38. [DOI] [PubMed] [PMC]
150. Mizuno T, Zhang G, Takeuchi H, Kawanokuchi J, Wang J, Sonobe Y, et al. Interferon-gamma directly induces neurotoxicity through a neuron specific, calcium-permeable complex of IFN-gamma receptor and AMPA GluR1 receptor. FASEB J. 2008;22:1797–806. [DOI] [PubMed]

151. Zou S, Li L, Pei L, Vukusic B, Van Tol HH, Lee FJ, et al. Protein-protein coupling/uncoupling enables dopamine $D_2$ receptor regulation of AMPA receptor-mediated excitotoxicity. J Neurosci. 2005;25:4385–95. [DOI] [PubMed] [PMC]
152. Lee FJ, Xue S, Pei L, Vukusic B, Chéry N, Wang Y, et al. Dual regulation of NMDA receptor functions by direct protein-protein interactions with the dopamine D1 receptor. Cell. 2002;111:219–30. [DOI] [PubMed]
153. Liu XY, Chu XP, Mao LM, Wang M, Lan HX, Li MH, et al. Modulation of D2R-NR2B interactions in response to cocaine. Neuron. 2006;52:897–909. [DOI] [PubMed]
154. Rodríguez-Muñoz M, Sánchez-Blázquez P, Vicente-Sánchez A, Berrocoso E, Garzón J. The mu-opioid receptor and the NMDA receptor associate in PAG neurons: implications in pain control. Neuropsychopharmacology. 2012;37:338–49. [DOI] [PubMed] [PMC]
155. Franco R, Rivas-Santisteban R, Casanovas M, Lillo A, Saura CA, Navarro G. Adenosine $A_{2A}$ Receptor Antagonists Affects NMDA Glutamate Receptor Function. Potential to Address Neurodegeneration in Alzheimer's Disease. Cells. 2020;9:1075. [DOI] [PubMed] [PMC]
156. Perroy J, Raynaud F, Homburger V, Rousset M, Telley L, Bockaert J, et al. Direct interaction enables cross-talk between ionotropic and group I metabotropic glutamate receptors. J Biol Chem. 2008;283:6799–805. [DOI] [PubMed]
157. Rodríguez-Ruiz M, Moreno E, Moreno-Delgado D, Navarro G, Mallol J, Cortés A, et al. Heteroreceptor Complexes Formed by Dopamine $D_1$, Histamine $H_3$, and *N*-Methyl-D-Aspartate Glutamate Receptors as Targets to Prevent Neuronal Death in Alzheimer's Disease. Mol Neurobiol. 2017;54:4537–50. [DOI] [PubMed]
158. Pandya NJ, Klaassen RV, van der Schors RC, Slotman JA, Houtsmuller A, Smit AB, et al. Group 1 metabotropic glutamate receptors 1 and 5 form a protein complex in mouse hippocampus and cortex. Proteomics. 2016;16:2698–705. [DOI] [PubMed] [PMC]
159. Wang X, Wang M, Xu T, Feng Y, Shao Q, Han S, et al. Structural insights into dimerization and activation of the mGlu2-mGlu3 and mGlu2-mGlu4 heterodimers. Cell Res. 2023;33:762–74. [DOI] [PubMed] [PMC]
160. Habrian CH, Levitz J, Vyklicky V, Fu Z, Hoagland A, McCort-Tranchepain I, et al. Conformational pathway provides unique sensitivity to a synaptic mGluR. Nat Commun. 2019;10:5572. [DOI] [PubMed] [PMC]
161. Kamikubo Y, Tabata T, Sakairi H, Hashimoto Y, Sakurai T. Complex formation and functional interaction between adenosine A1 receptor and type-1 metabotropic glutamate receptor. J Pharmacol Sci. 2015;128:125–30. [DOI] [PubMed]
162. González-Maeso J, Ang RL, Yuen T, Chan P, Weisstaub NV, López-Giménez JF, et al. Identification of a serotonin/glutamate receptor complex implicated in psychosis. Nature. 2008;452:93–7. [DOI] [PubMed] [PMC]
163. Ferré S, Karcz-Kubicha M, Hope BT, Popoli P, Burgueño J, Gutiérrez MA, et al. Synergistic interaction between adenosine A2A and glutamate mGlu5 receptors: implications for striatal neuronal function. Proc Natl Acad Sci U S A. 2002;99:11940–5. [DOI] [PubMed] [PMC]
164. Tebano MT, Martire A, Rebola N, Pepponi R, Domenici MR, Grò MC, et al. Adenosine $A_{2A}$ receptors and metabotropic glutamate 5 receptors are co-localized and functionally interact in the hippocampus: a possible key mechanism in the modulation of *N*-methyl-D-aspartate effects. J Neurochem. 2005;95:1188–200. [DOI] [PubMed]
165. Popoli P, Pèzzola A, Torvinen M, Reggio R, Pintor A, Scarchilli L, et al. The selective $mGlu_5$ receptor agonist CHPG inhibits quinpirole-induced turning in 6-hydroxydopamine-lesioned rats and modulates the binding characteristics of dopamine $D_2$ receptors in the rat striatum: interactions with adenosine $A_{2a}$ receptors. Neuropsychopharmacology. 2001;25:505–13. [DOI] [PubMed]

166. Schröder H, Wu DF, Seifert A, Rankovic M, Schulz S, Höllt V, et al. Allosteric modulation of metabotropic glutamate receptor 5 affects phosphorylation, internalization, and desensitization of the micro-opioid receptor. Neuropharmacology. 2009;56:768–78. [DOI] [PubMed]
167. Ferre S, Ciruela F, Borycz J, Solinas M, Quarta D, Antoniou K, et al. Adenosine $A_1$-$A_{2A}$ receptor heteromers: new targets for caffeine in the brain. Front Biosci. 2008;13:2391–9. [DOI] [PubMed]
168. Liu F, Wan Q, Pristupa ZB, Yu XM, Wang YT, Niznik HB. Direct protein-protein coupling enables cross-talk between dopamine D5 and gamma-aminobutyric acid A receptors. Nature. 2000;403:274–80. [DOI] [PubMed]
169. Batalha VL, Ferreira DG, Coelho JE, Valadas JS, Gomes R, Temido-Ferreira M, et al. The caffeine-binding adenosine $A_{2A}$ receptor induces age-like HPA-axis dysfunction by targeting glucocorticoid receptor function. Sci Rep. 2016;6:31493. [DOI] [PubMed] [PMC]
170. Mifsud KR, Reul JM. Acute stress enhances heterodimerization and binding of corticosteroid receptors at glucocorticoid target genes in the hippocampus. Proc Natl Acad Sci U S A. 2016;113:11336–41. [DOI] [PubMed] [PMC]
171. Dewing P, Boulware MI, Sinchak K, Christensen A, Mermelstein PG, Micevych P. Membrane estrogen receptor-alpha interactions with metabotropic glutamate receptor 1a modulate female sexual receptivity in rats. J Neurosci. 2007;27:9294–300. [DOI] [PubMed] [PMC]
172. Pelassa S, Guidolin D, Venturini A, Averna M, Frumento G, Campanini L, et al. A2A-D2 Heteromers on Striatal Astrocytes: Biochemical and Biophysical Evidence. Int J Mol Sci. 2019;20:2457. [DOI] [PubMed] [PMC]
173. Tonazzini I, Trincavelli ML, Montali M, Martini C. Regulation of $A_1$ adenosine receptor functioning induced by $P2Y_1$ purinergic receptor activation in human astroglial cells. J Neurosci Res. 2008;86:2857–66. [DOI] [PubMed]
174. Amato S, Averna M, Guidolin D, Pedrazzi M, Pelassa S, Capraro M, et al. Heterodimer of A2A and Oxytocin Receptors Regulating Glutamate Release in Adult Striatal Astrocytes. Int J Mol Sci. 2022;23:2326. [DOI] [PubMed] [PMC]
175. Amato S, Averna M, Guidolin D, Ceccoli C, Gatta E, Candiani S, et al. Heteromerization of Dopamine D2 and Oxytocin Receptor in Adult Striatal Astrocytes. Int J Mol Sci. 2023;24:4677. [DOI] [PubMed] [PMC]
176. Guo C, Masin M, Qureshi OS, Murrell-Lagnado RD. Evidence for functional $P2X_4$/$P2X_7$ heteromeric receptors. Mol Pharmacol. 2007;72:1447–56. [DOI] [PubMed]
177. Callén L, Moreno E, Barroso-Chinea P, Moreno-Delgado D, Cortés A, Mallol J, et al. Cannabinoid receptors $CB_1$ and $CB_2$ form functional heteromers in brain. J Biol Chem. 2012;287:20851–65. [DOI] [PubMed] [PMC]
178. Franco R, Reyes-Resina I, Aguinaga D, Lillo A, Jiménez J, Raïch I, et al. Potentiation of cannabinoid signaling in microglia by adenosine $A_{2A}$ receptor antagonists. Glia. 2019;67:2410–23. [DOI] [PubMed]
179. Reyes-Resina I, Navarro G, Aguinaga D, Canela EI, Schoeder CT, Załuski M, et al. Molecular and functional interaction between GPR18 and cannabinoid $CB_2$ G-protein-coupled receptors. Relevance in neurodegenerative diseases. Biochem Pharmacol. 2018;157:169–79. [DOI] [PubMed]
180. Nicoletti F, Di Menna L, Iacovelli L, Orlando R, Zuena AR, Conn PJ, et al. GPCR interactions involving metabotropic glutamate receptors and their relevance to the pathophysiology and treatment of CNS disorders. Neuropharmacology. 2023;235:109569. [DOI] [PubMed]
181. Liu J, Zhang Z, Moreno-Delgado D, Dalton JA, Rovira X, Trapero A, et al. Allosteric control of an asymmetric transduction in a G protein-coupled receptor heterodimer. Elife. 2017;6:e26985. [DOI] [PubMed] [PMC]
182. Murat S, Bigot M, Chapron J, König GM, Kostenis E, Battaglia G, et al. 5-$HT_{2A}$ receptor-dependent phosphorylation of $mGlu_2$ receptor at Serine 843 promotes $mGlu_2$ receptor-operated $G_{i/o}$ signaling. Mol Psychiatry. 2019;24:1610–26. [DOI] [PubMed]

183. Pisani A, Gubellini P, Bonsi P, Conquet F, Picconi B, Centonze D, et al. Metabotropic glutamate receptor 5 mediates the potentiation of *N*-methyl-D-aspartate responses in medium spiny striatal neurons. Neuroscience. 2001;106:579–87. [DOI] [PubMed]
184. Husi H, Ward MA, Choudhary JS, Blackstock WP, Grant SG. Proteomic analysis of NMDA receptor-adhesion protein signaling complexes. Nat Neurosci. 2000;3:661–9. [DOI] [PubMed]
185. Scholler P, Nevoltris D, de Bundel D, Bossi S, Moreno-Delgado D, Rovira X, et al. Allosteric nanobodies uncover a role of hippocampal mGlu2 receptor homodimers in contextual fear consolidation. Nat Commun. 2017;8:1967. [DOI] [PubMed] [PMC]
186. Borroto-Escuela DO, Rodriguez D, Romero-Fernandez W, Kapla J, Jaiteh M, Ranganathan A, et al. Mapping the Interface of a GPCR Dimer: A Structural Model of the $A_{2A}$ Adenosine and $D_2$ Dopamine Receptor Heteromer. Front Pharmacol. 2018;9:829. [DOI] [PubMed] [PMC]
187. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera—a visualization system for exploratory research and analysis. J Comput Chem. 2004;25:1605–12. [DOI] [PubMed]
188. de Mendonça A, Sebastião AM, Ribeiro JA. Adenosine: does it have a neuroprotective role after all? Brain Res Brain Res Rev. 2000;33:258–74. [DOI] [PubMed]
189. Fuxe K, Marcellino D, Genedani S, Agnati L. Adenosine $A_{2A}$ receptors, dopamine $D_2$ receptors and their interactions in Parkinson's disease. Mov Disord. 2007;22:1990–2017. [DOI] [PubMed]
190. Tozzi A, Tscherter A, Belcastro V, Tantucci M, Costa C, Picconi B, et al. Interaction of A2A adenosine and D2 dopamine receptors modulates corticostriatal glutamatergic transmission. Neuropharmacology. 2007;53:783–9. [DOI] [PubMed]
191. Guidolin D, Marcoli M, Tortorella C, Maura G, Agnati LF. Adenosine $A_{2A}$-dopamine $D_2$ receptor-receptor interaction in neurons and astrocytes: Evidence and perspectives. Prog Mol Biol Transl Sci. 2020;169:247–77. [DOI] [PubMed]
192. Ferre S, von Euler G, Johansson B, Fredholm BB, Fuxe K. Stimulation of high-affinity adenosine A2 receptors decreases the affinity of dopamine D2 receptors in rat striatal membranes. Proc Natl Acad Sci U S A. 1991;88:7238–41. [DOI] [PubMed] [PMC]
193. Kull B, Ferré S, Arslan G, Svenningsson P, Fuxe K, Owman C, et al. Reciprocal interactions between adenosine A2A and dopamine D2 receptors in Chinese hamster ovary cells co-transfected with the two receptors. Biochem Pharmacol. 1999;58:1035–45. [DOI] [PubMed]
194. Fernández-Dueñas V, Gómez-Soler M, Jacobson KA, Kumar ST, Fuxe K, Borroto-Escuela DO, et al. Molecular determinants of $A_{2A}$R-$D_2$R allosterism: role of the intracellular loop 3 of the $D_2$R. J Neurochem. 2012;123:373–84. [DOI] [PubMed] [PMC]
195. Dominguez R, Micevych P. Estradiol rapidly regulates membrane estrogen receptor alpha levels in hypothalamic neurons. J Neurosci. 2010;30:12589–96. [DOI] [PubMed] [PMC]
196. Guidolin D, Tortorella C, Marcoli M, Cervetto C, Maura G, Agnati LF. Receptor-Receptor Interactions and Glial Cell Functions with a Special Focus on G Protein-Coupled Receptors. Int J Mol Sci. 2021;22:8656. [DOI] [PubMed] [PMC]
197. Cervetto C, Venturini A, Passalacqua M, Guidolin D, Genedani S, Fuxe K, et al. A2A-D2 receptor-receptor interaction modulates gliotransmitter release from striatal astrocyte processes. J Neurochem. 2017;140:268–79. [DOI] [PubMed]
198. McNeill J, Rudyk C, Hildebrand ME, Salmaso N. Ion Channels and Electrophysiological Properties of Astrocytes: Implications for Emergent Stimulation Technologies. Front Cell Neurosci. 2021;15:644126. [DOI] [PubMed] [PMC]
199. Fitzner D, Bader JM, Penkert H, Bergner CG, Su M, Weil MT, et al. Cell-Type- and Brain-Region-Resolved Mouse Brain Lipidome. Cell Rep. 2020;32:108132. [DOI] [PubMed]
200. Tewari M, Michalski S, Egan TM. Modulation of Microglial Function by ATP-Gated P2X7 Receptors: Studies in Rat, Mice and Human. Cells. 2024;13:161. [DOI] [PubMed] [PMC]

201. Trang M, Schmalzing G, Müller CE, Markwardt F. Dissection of P2X4 and P2X7 Receptor Current Components in BV-2 Microglia. Int J Mol Sci. 2020;21:8489. [DOI] [PubMed] [PMC]
202. Tanaka M, Sackett S, Zhang Y. Endocannabinoid Modulation of Microglial Phenotypes in Neuropathology. Front Neurol. 2020;11:87. [DOI] [PubMed] [PMC]
203. Young AP, Denovan-Wright EM. The Dynamic Role of Microglia and the Endocannabinoid System in Neuroinflammation. Front Pharmacol. 2022;12:806417. [DOI] [PubMed] [PMC]
204. Stella N. Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. Glia. 2010;58:1017–30. [DOI] [PubMed] [PMC]
205. Lewerenz J, Maher P. Chronic Glutamate Toxicity in Neurodegenerative Diseases-What is the Evidence? Front Neurosci. 2015;9:469. [DOI] [PubMed] [PMC]
206. Doble A. The role of excitotoxicity in neurodegenerative disease: implications for therapy. Pharmacol Ther. 1999;81:163–221. [DOI] [PubMed]