Russian Chemical Reviews **78** (5) 485 – 494 (2009) © 2009 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2009v078n05ABEH004020

Modern approaches to the design of memory and cognitive enhancers based on AMPA receptor ligands

V V Grigoriev, A N Proshin, A S Kinzirsky, S O Bachurin

Contents

I.	Introduction	485
II.	Structure of AMPA receptors	485
III.	Agonists, antagonists and negative modulators	486
IV.	Modern views on the mechanisms of deactivation and desensitization of AMPA receptors	487
V.	Positive modulators of AMPA receptors: chemical classes and mechanisms of action	489

Abstract. Data on the structure and properties of compounds acting on AMPA receptors, the key subtype of ionotropic glutamate receptors of the mammalian central nervous system, are analyzed. Data on the role of these receptors in provision of memory and cognitive function formation and impairment processes are presented. The attention is focused on the modern views on the mechanisms of AMPA receptor desensitization and deactivation and action of substances affecting these processes. The structures of key positive modulators of AMPA receptors are given. The problems of application of these substances as therapeutic agents for preventing and treating neurodegenerative and psychoneurological diseases are discussed. The bibliography includes 121 references.

I. Introduction

The glutamatergic neurotransmitter system is the main excitatory neurotransmitter circuit of mammal brain, and glutamatergic synapses make the vast majority among all excitatory synapses.[1] Glutamate receptors can be divided into two main classes: ionotropic and metabotropic receptors.[2] The activation of ionotropic receptors with an agonist induces their conformational changes and results in opening of the ion channel. The activation of metabotropic receptors is related to G-protein activation and subsequent activation of phospholipase C or inhibition of adenylate cyclase activity.[3] Ionotropic glutamate receptors are classified into three types according to the name of the selective agonist, which include 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA receptors), *N*-methyl-D-aspartic acid (NMDA receptors) and kainic acid (kainate receptors).[4]

In recent years, compounds (ligands) that can bind to AMPA receptors have attracted attention of researchers as new medical drugs for treating some neurodegenerative and psychoneurological disorders such as Alzheimer's and Parkinson's diseases, schizophrenia, mental depression, epilepsy, amyotrophic lateral sclerosis, disseminated sclerosis, mild cognitive impairment, age-related cognitive and memory dysfinctions.[5–12] Among various types of AMPA receptor ligands, so-called positive modulators (or potentiators), which improve memory and cognitive functions of humans and animals, have aroused particular interest in recent years.[13] This group of potential medical drugs is in the focus of attention in this review.

II. Structure of AMPA receptors

AMPA receptors comprise four types of subunits, GluR1, GluR2, GluR3 and GluR4, which are encoded by separate genes.[14] Native AMPA receptors are tetramers and usually comprise a combination of several subunits (Fig. 1).[15, 16]

Each subunit of ionotropic glutamate receptors contains three transmembrane domains, A, B and C (in another terminology, M1, M3 and M4). Also, there are extracellular N-terminal and intracellular C-terminal domains with a ligand-binding chelate domain between them formed by the S1 and S2 'loops'. The ligand (glutamate) binds to the receptor inside these loops.

The ion channel domain is embedded in the membrane from the cell side and forms a hairpin-like structure (Fig. 2).[17] The channel is permeable for singly (Na^+, K^+) and doubly charged (Ca^{2+}) cations. The GluR2 subunit plays an important role, as its presence in the receptor prevents calcium ions from entering the neuron through heteromeric receptors. The AMPA receptors devoid of the GluR2 subunit conduct calcium ions.[18, 19] The appropriate structures of two subunits form a dimer. Native AMPA receptors are composed of two dimers.[20]

V V Grigoriev, A N Proshin, A S Kinzirsky, S O Bachurin Institute of Physiologically Active Compounds, Russian Academy of Sciences, pr. Severnyi 1, 142432 Chernogolovka Moscow Region, Russian Federation. Fax (7-496) 524 95 08, tel. (7-496) 524 25 16, e-mail: grigor@ipac.ac.ru (V V Grigoriev), tel. (7-496) 524 26 11, e-mail: proshin@ipac.ac.ru (A N Proshin), tel. (7-499) 972 14 80, e-mail: alex.kinzirsky@ipac.ac.ru (A S Kinzirsky), tel. (7-496) 524 95 08, e-mail: bachurin@ipac.ac.ru (S O Bachurin)

Received 11 January 2009
Uspekhi Khimii **78** (5) 524 – 534 (2009); translated by Z P Svitanko

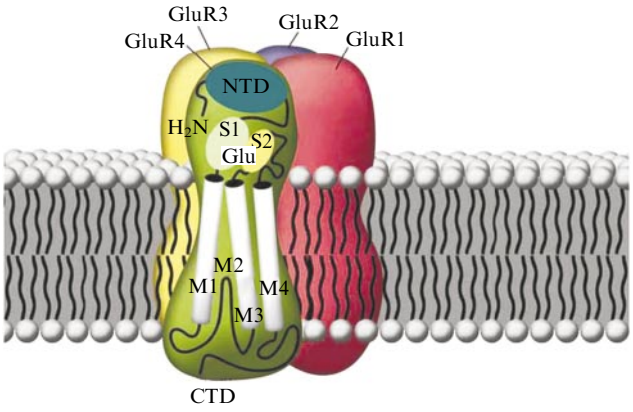


Figure 1. Structure of the AMPA receptor.[16]
M1, M3 and M4 are transmembrane domains, M2 is the intramembrane domain of the ion channel; NTD is N-terminal domain, S1 – S2 is the 'pocket' for agonist (glutamate) binding; CTD is the C-terminal domain.

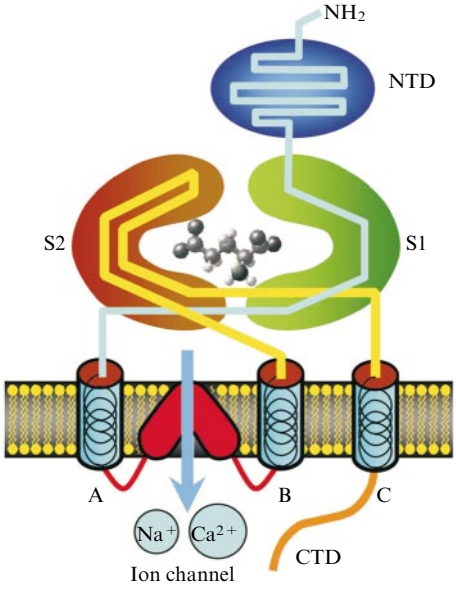


Figure 2. Structure of a glutamate receptor subunit.[17]
The transmembrane regions are defined as A, B and C; NTD is the extracellular N-terminal domain; CTD is the intracellular C-terminal domain; S1 – S2 is the 'pocket' with the binding site of glutamate and other agonists.

The functional multiplicity of AMPA receptors is provided by the variety of subunit combinations in them. In addition, all of the four subunits of AMPA receptors occur as two alternative forms, flip and flop forms, which are encoded by exons 14 and 15 (in the GluR2 subunit) located ahead of the transmembrane domain M4.[21, 22] In these forms, replacements of the amino acids take place in particular sites of the S2 segment (Fig. 3). Flip versions predominate in the prenatal period of organism development and continue to be expressed in the adult state, whereas flop variants are very few in the first week after birth but their number increases with time, and in the adult state both variants are equally abundant.

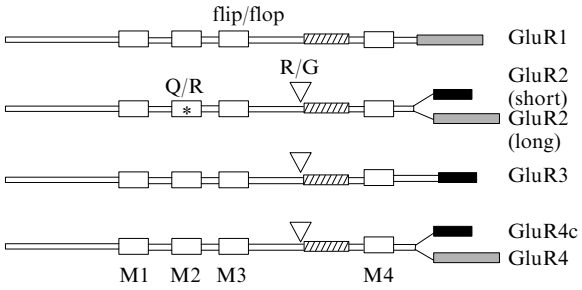


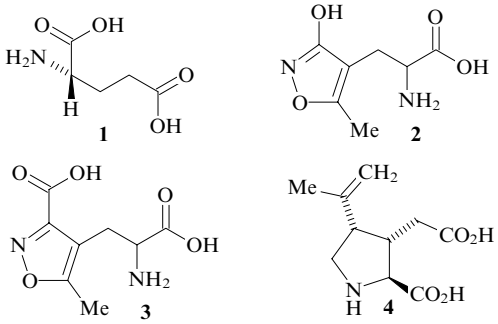
Figure 3. Possible alternative versions of synthesis of AMPA receptor subunits.[4]
The flip/flop and C-terminal alternatives of AMPA receptor subunits are shown schematically; the subunit regions located in the membrane are shown by rectangles M1 – M4; Q/R and R/G are regions with possible different amino acid sequences.

The additional diversity of receptors is caused by post-scription alterations — alternative splicing and RNA editing.[23, 24] Certain amino acid replacements (Q or R, R or G) are encountered in subunits and change their properties. Different C-terminal variants were detected in the GluR2 and GluR4 subunits (see Fig. 3).[4] In view of the foregoing, the diversity of AMPA receptors becomes understandable.

III. Agonists, antagonists and negative modulators

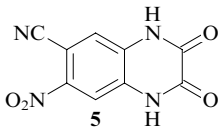
1. Agonists

Depending on their ability to induce conformational changes in the ligand-binding domain, the S1 – S2 pocket, and the accompanying changes in the degree of desensitization of the AMPA receptor, agonists can be full or partial. Full agonists of AMPA receptors are glutamic acid (**1**), AMPA (**2**), quisqualic acid and 2-amino-3-(3-carboxy-5-methylisoxazol-4-yl)propionic acid (ACPA) (**3**). Kainic acid (**4**) is a partial agonist.[25] Full agonists induce the maximum conformational changes (and, as a consequence, maximum opening of the ion channel) and the maximum receptor desensitization; partial agonists cause incomplete conformational change and partial desensitization.[25, 26]

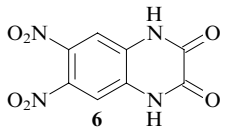


2. Competitive antagonists

In the 1980s, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) (**5**) and 6,7-dinitroquinoxaline-2,3-dione (DNQX) (**6**) were proposed as selective and active competitive AMPA receptor antagonists.[27]

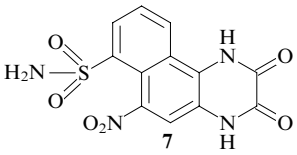


5

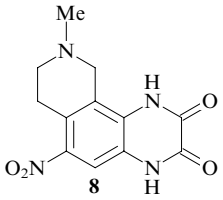


6

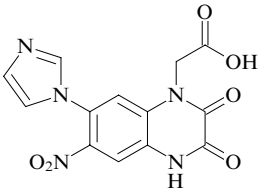
However, these compounds proved also to be active with respect to the glycine region of the NMDA receptor and, hence, they were not selective antagonists.[28] Nevertheless, they served as prototype substances for the synthesis of more selective and active antagonists in the quinoxaline series such as 6-nitro-7-sulfamoylbenzo[*f*]quinoxaline-2,3-dione (NBQX) (**7**);[29] 9-methyl-6-nitro-8,10-dihydropyrido[3,4-*f*]quinoxaline-2,3(7*H*)-dione (PNQX) (**8**), 6-(1*H*-imidazol-1-yl)-7-nitroquinoxaline-2,3-dione (YM-90K);[30] [7-(imidazol-1-yl)-6-nitro-2,3-dioxoquinoxalin-1-yl]acetic acid (**9**)[31] and 7-(morpholin-4-yl)-2,3-dioxo-6-trifluoromethylquinoxalin-1-yl)methylphosphonic acid (**10**).[32]



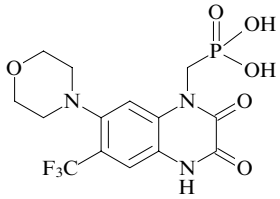
7



8



9 (YM-872)†

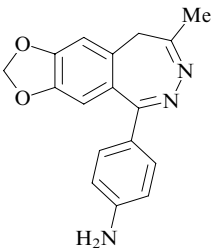


10 (ZR-200775)

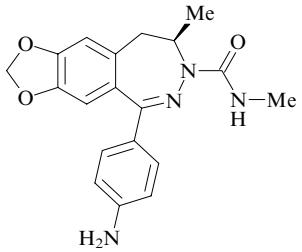
Compounds **9** and **10** were passed to clinical trials as anti-stroke drugs.[33]

3. Non-competitive antagonists

Non-competitive antagonists of AMPA receptors are represented by allosteric negative modulators. Some of them refer to the class of 2,3-benzodiazepines. These include 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (**11**), which was the first to be synthesized in this class of compound,[34] (*R*)-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-3-methylcarbamoyl-4,5-dihydro-2,3-benzodiazepine (**12**) and (*R*)-3-acetyl-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-2,3-benzodiazepine (**13**).[35]

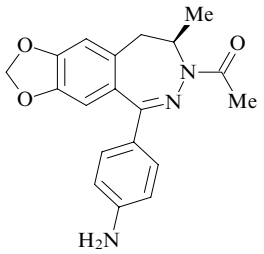


11 (GYKI-52466)



12 (GYKI-53784/LY-303070)

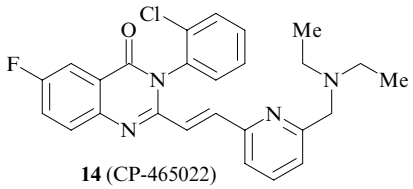
† Here and below the commercial code of the compound is given in parentheses after its number.



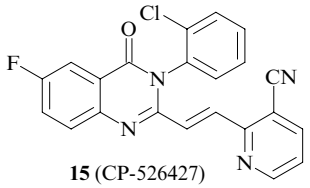
13 (GYKI-53773/LY-300164)

These compounds have low selectivity towards AMPA receptor subtypes but are more selective towards AMPA receptors *versus* kainate or NMDA receptors.[35,36] They penetrate the blood–brain barrier and are active in the systemic administration.[37] Compound **13** (talampanel) was proposed for clinical trials as an antiepileptic agent.[38,39]

A number of another class of derivatives, quinazolinones, are also selective non-competitive antagonists of AMPA receptors. The most active among these are 3-(2-chlorophenyl)-2-[(*E*)-2-(6-diethylaminopyridin-2-yl)-vinyl]-6-fluoroquinazolin-4(3*H*)-one (**14**) and 2-{(*E*)-2-[3-(2-chlorophenyl)-6-fluoro-4-oxo-3,4-dihydroquinazolin-2-yl]vinyl}nicotinonitrile (**15**).[40,41]



14 (CP-465022)



15 (CP-526427)

In binding experiments of tritium-labelled compound **15**, it competed with the 2,3-benzodiazepine binding sites.[42] These compounds also penetrate the blood–brain barrier, they are active in the systemic administration and also non-selective relative to AMPA receptor subunits.[43]

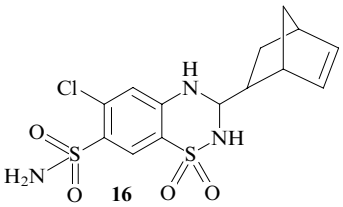
IV. Modern views on the mechanisms of deactivation and desensitization of AMPA receptors

Transition of AMPA receptors to an 'inactive state' may be induced by two processes: deactivation and desensitization. Deactivation is caused by closure of the ion channel upon removal of the agonist. Desensitization implies inability of the receptor to pass once again into the activated (open ion channel) state, despite the presence of an agonist. Desensitization and deactivation of AMPA receptors are very fast; these factors can affect the magnitude and kinetics of the synaptic current mediated through activation of AMPA receptors.[44]

The rate of desensitization of AMPA receptors depends on their subunit composition and subunit modifications (flip or flop).[45] Homomeric AMPA receptors composed of GluR3flop or GluR4flop are desensitized 3–5 times faster

than other homomeric receptors; the introduction of GluR2flop accelerates desensitization of flip variants. In addition, an alternative synthesis of the R/G region located above the flip/flop region can accelerate up to twice the restoration after desensitization, depending on the subunit composition.[46] The allosteric transitions, which lead to desensitization, depend, in particular, on the structure of the agonist interacting with the receptor. For example, AMPA or glutamate induce much faster and more complete desensitization of AMPA receptors than kainic acid.[25]

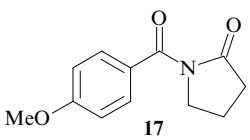
The decrease in desensitization of AMPA receptors by positive modulators plays an important role in improving the learning ability and memory; therefore, the desensitization and deactivation mechanisms have been investigated.[47,48] Figure 4 (see page 490) shows three-dimensional models of AMPA receptors isolated from synapses of hippocampus CA1 field.[49] The models were designed using electron microscopic images of native AMPA receptors with deposited silver particles. One can clearly see N-terminal domains (NTD_2) and ligand-binding domains (LBD_2) combined into dimers and transmembrane domains (TMD_2) combined into tetramers. AMPA receptors were found in two types of conformations: type I, NTD_2 dimers are partly twisted; type II, NTD_2 dimers are separated. In the 'resting state', AMPA receptors of type I accounted for $\sim$60% and type II receptors accounted for 40% of their total number. The addition of glutamate (1 mmol litre^{-1}) caused a considerable change in the ratio of different types of AMPA receptors: there was only 3% type I receptors and 97% type II receptors. If glutamate was added together with 3-(bicyclo[2.2.1]hept-2-en-6-yl)-6-chloro-1,1-dioxo-3,4-dihydro-2*H*-benzo[*e*]-1,2,4-thiadiazine-7-sulfamide (**16**) (cyclothiazide), which inhibits desensitization of AMPA receptors, much less receptors of type I passed to the conformation of type II, in particular, 49% of the receptors remained in the type I conformation.



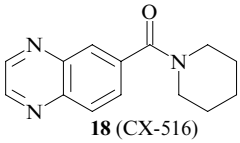
16

Thus, the conformational state of the AMPA receptors determines their functional state: type I conformation corresponds to the non-desensitized receptor, while the conformation of type II corresponds to desensitized receptor. A potentiator of AMPA receptors such as cyclothiazide stabilizes AMPA receptor dimers in the twisted ligand-bound state where the ion channel is open.

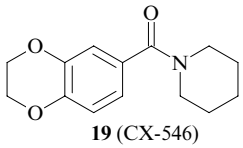
Jin *et al.*[50] elucidated the difference in the mechanisms of action of compounds like cyclothiazide, which inhibit desensitization, and 1-(4-methoxybenzoyl)-2-pyrrolidone (**17**) (aniracetam) and its analogues — 6-(piperidin-1-ylcarbonyl)quinoxaline (**18**), 6-(piperidin-1-yl)carbonyl-2,3-dihydro-1,4-benzodioxin (**19**), 2*H*,5*aH*-pyrrolidino[2,1-3′,2′]-1,3-oxazino[6′,5′-5,4]benzo[*d*]-1,3-dioxolan-9-one (**20**), 2*H*,3*H*,6*aH*-pyrrolidino[2,1-3′,2′]-1,3-oxazino[6′,5′-5,4]benzo[*e*]-1,4-dioxan-10-one (**21**), which retard deactivation.



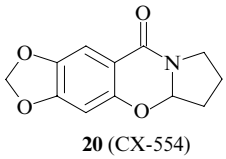
17



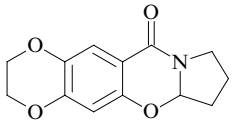
18 (CX-516)



19 (CX-546)



20 (CX-554)



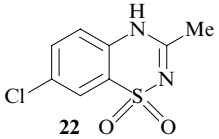
21 (CX-614)

The mechanism of action of the latter compounds is as follows. One molecule of, for example, compound **21** is embedded into the space ('pocket') between the S1 and S2 loops of the ligand-binding domain and fix it in the closed ('operating') state. Two molecules of a compounds that inhibits desensitization are inserted in the slit between two S1 – S2 pockets and fix the interslit space, thus preventing the dimer from changing the position. As a result, desensitization decreases (Fig. 5, see page 490).[50]

Thus, some compounds (for example, **19** – **21**) are able to affect simultaneously both deactivation and desensitization, despite the difference between these processes.[50–52] The deactivation and desensitization of AMPA receptors play an important role in the regulation of their functional state, and, as a consequence, in the character of synaptic transmission, strength and properties of synaptic plasticity, which form the material base of memory and cognitive functions. Therefore, in recent years considerable attention has been paid to the search for new potentiators of AMPA receptors, medicinal drugs and cognitive stimulants.

V. Positive modulators of AMPA receptors: chemical classes and mechanisms of action

Positive modulators of AMPA receptors increase the synaptic current and long-term potentiation of the synaptic transmission and hence they have beneficial effect on the memory and cognitive functions.[13,53–55] Positive modulators (or potentiators) of AMPA receptors were discovered occasionally in a study of the mechanism of action of nootropics: one of these compounds, aniracetam (**17**), was found to enhance AMPA receptor responses (currents).[56] Then it was shown that chemically absolutely different compounds, benzothiadiazines such as-7-chloro- 3-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (diazoxide) (**22**), and cyclothiazide (**16**) also potentiate responses of AMPA receptors.[57,58]



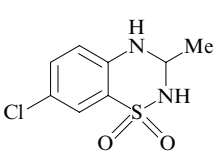
22

In the study of AMPA receptors, aniracetam and cyclothiazide were used as model positive modulators but they have scarcely found any therapeutic use due to the very fast

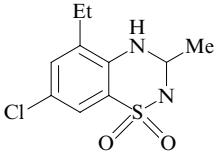
metabolic degradation of aniracetam and low penetrability of cyclothiazide through the blood–brain barrier.[59]

In the 1990s Cortex Pharmaceutics synthesized bioisosteric analogues of aniracetam called AMPAkins™. The highest activity among them was found for compounds **18**–**21**.[51, 52, 60–62]

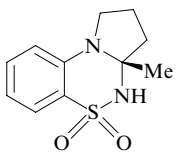
In turn, the synthesis of new derivatives of the benzothiadiazines revealed more active compounds: 7-chloro-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**23**);[63, 64] 7-chloro-5-ethyl-3-methyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**24**) (see Ref. 65) and (*S*)-3*a*-methyl-2,3,3*a*,4-tetrahydro-1*H*-benzo[*e*]pyrrolo[2,1-*c*]-1,2,4-thiadiazine 5,5-dioxide (**25**).[66]



23 (IDRA-21)



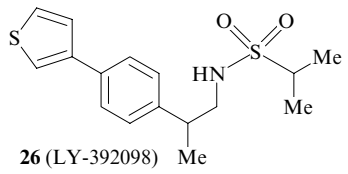
24 (D-1)



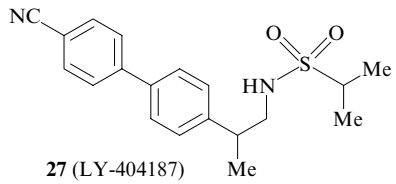
25 (S-18986-1)

Later, a new class of compounds capable of positive modulation of AMPA receptors was found, namely, biarylpropylsulfamides[67, 68] and their analogues.

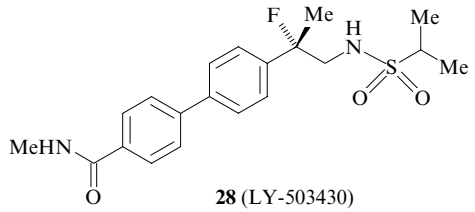
The best known biarylpropylsulfamide potentiators of AMPA receptors are as follows: *N*-{2-[4-(3-thienyl)phenyl]-propyl}propane-2-sulfamide (**26**), *N*-[2-(4′-cyanobiphenyl-4-yl)propyl]propane-2-sulfamide (**27**), 4′-{(1*R*)-1-fluoro-1-methyl-2-[(propan-2-ylsulfonyl)amino]ethyl}-*N*-methylbiphenyl-4-carboxamide (**28**),[7, 69–71] {(3*S*,4*R*)-4-[3′-(*N*-methylsulfonyl-*N*-methylamino)biphenyl-4-yl]-1-methyl-3-(propane-2-sulfamido)pyrrolidine (**29**), *N*-{(1*S*,2*R*)-2-[4-(6-fluoro-3-pyridyl)phenyl]cyclopropyl}propane-2-sulfamide (**30**).[16]



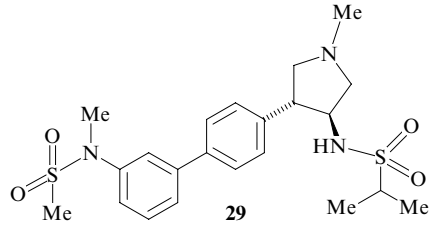
26 (LY-392098)



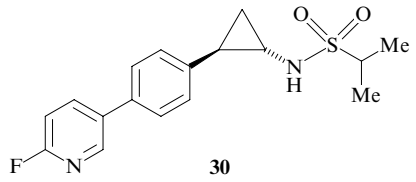
27 (LY-404187)



28 (LY-503430)

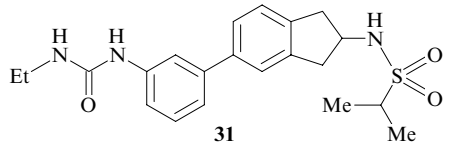


29

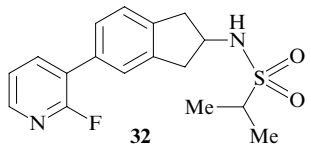


30

In 2006, new sulfamide derivatives were proposed by Glaxo Ltd. as potentiators of AMPA receptors, namely, *N*-{5-[3-(3-ethylureido)phenyl]indan-2-yl}propane-2-sulfamide (**31**) and *N*-[5-(2-fluoro-3-pyridyl)indan-2-yl]propane-2-sulfamide (**32**).[16]

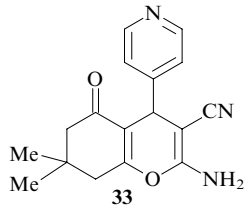


31

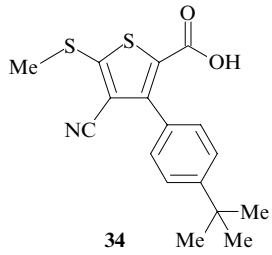


32

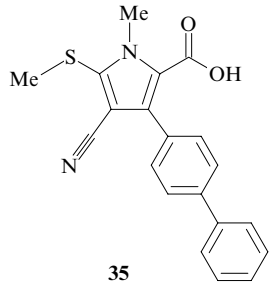
The ability of potentiation of AMPA receptors was also found for representatives of other classes of compounds: 2-amino-7,7-dimethyl-5-oxo-4-(4-pyridyl)-5,6,7,8-tetrahydro-4-*H*-chromene-3-carbonitrile (**33**),[16] 4-cyano-5-methylthio-3-(4-*tert*-butylphenyl)thiophene-2-carboxylic acid (**34**) and 3-(biphenyl-4-yl)-1-methyl-5-methylthio-4-cyanopyrrole-2-carboxylic acid (**35**), which were synthesized by Eli Lilly.[72, 73]



33

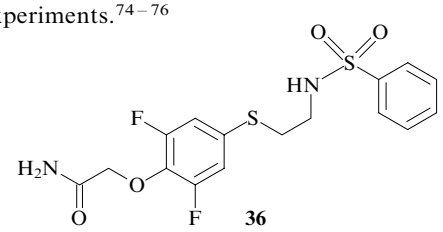


34



35

An (*N*-ethyl)phenylsulfamide derivative, 2-[2,6-difluoro-4-(3-phenylsulfonylaminopropyl)phenoxy]acetamide (PEPA) (**36**) also potentiates AMPA receptors and enhances the memory of animals, which was demonstrated in behaviour experiments.[74–76]



36

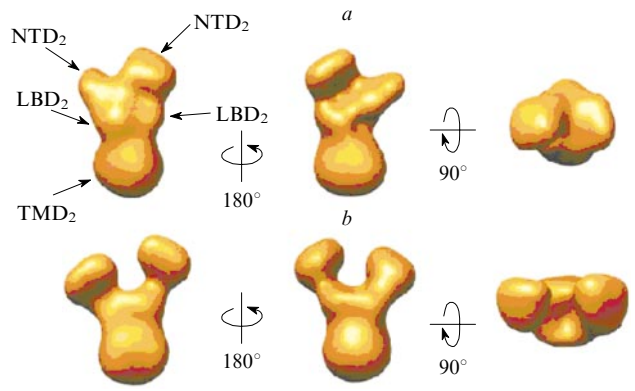


Figure 4. Three-dimensional model of AMPA receptors based on electron microscopic images of native AMPA receptors coloured by silver particles.[49]
(*a*) AMPA receptors in conformation of type I, which corresponds to the non-desensitized state of the receptor: NTD_2 dimers are in twisted state; (*b*) AMPA receptors in conformation of type II, which corresponds to the desensitized state of the receptor: NTD_2 dimers are separated.

The action of positive modulators on the synaptic transmission and kinetics of AMPA receptors was studied. It was found that the potentiating action of these substances is accomplished through different mechanisms. AMPAkins can affect receptor activation/deactivation and desensitization processes. Compounds such as **19**–**21** decelerate closure of ion channels, *i.e.*, inhibit deactivation of AMPA receptors.[51, 52, 65] Apparently, the mechanism of action of compound **18**, resulting in potentiation of currents of AMPA receptors, differs from the mechanism of action of aniracetam or compound **21**. In binding experiments of tritium-labelled AMPA and 5-fluorovillardine, compound **18** did not enhance their binding and also did not interact with the binding sites of other potentiators of AMPA receptors such as **1** and **19**.[77] The results of computer simulation experiments of the physiological action of compound **18** on the parameters of the AMPA receptor currents led Arai *et al.*[65] to conclusion that this compound potentiates the currents most likely by accelerating opening of ion channels rather than by inhibiting deactivation.

AMPAkins (except for compound **18**) can also affect desensitization process by decelerating it with different degrees of efficiency. Cyclothiazide affects only desensitiza-

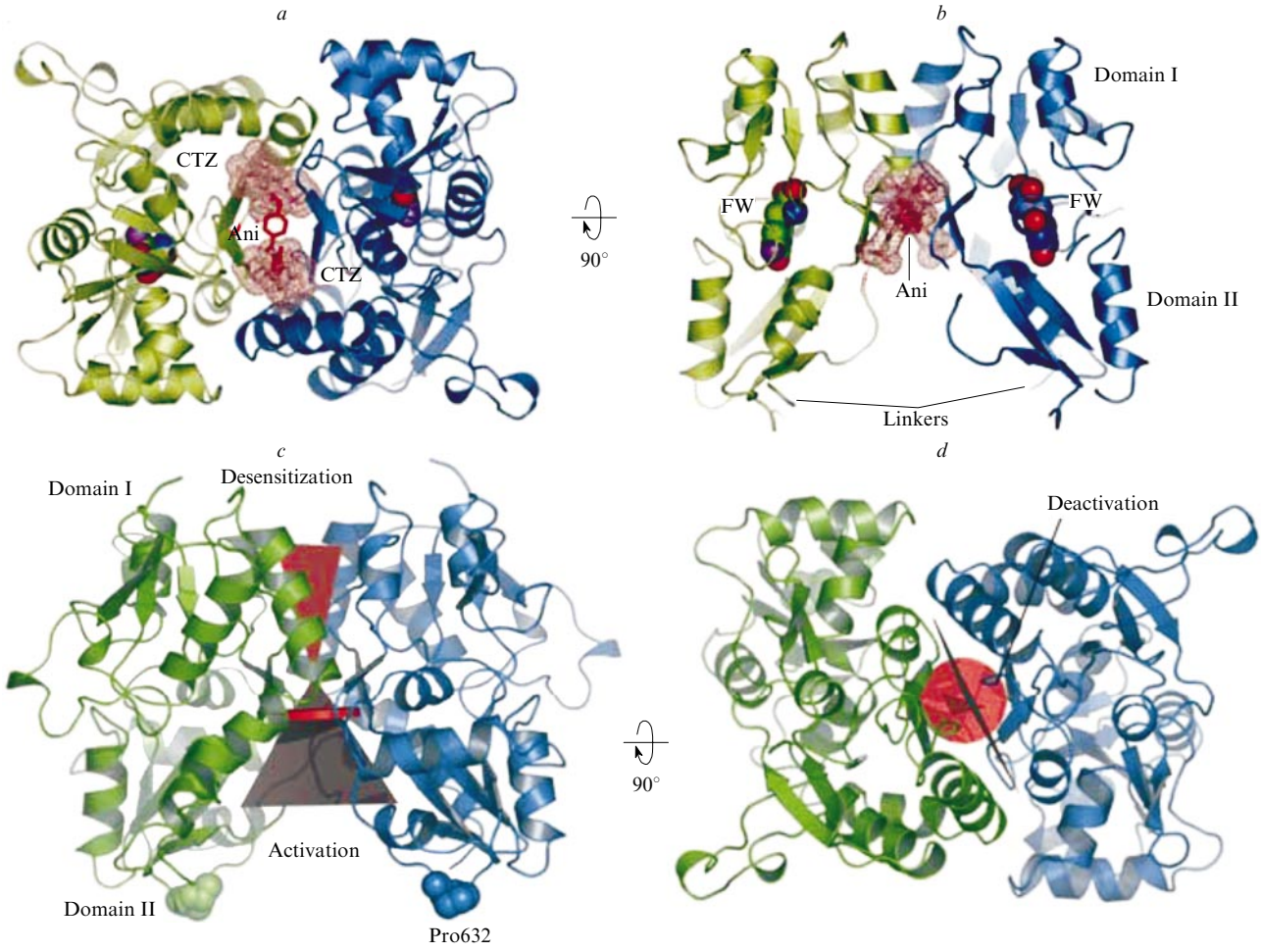


Figure 5. Binding sites of aniracetam and cyclothiazide.[50]
(*a*) dimer top view. Blue color marks the S1 – S2 'pocket' of one subunits, green color, of the other subunit; red and blue spheres are molecules of the agonist, 5-fluorowillardiine (FW). The dimer slit accommodates the built-in aniracetam (Ani) molecule or two cyclothiazide molecules (CTZ) (superimposed); (*b*) dimer view with 90° rotation; (*c*) on deactivation, the subunits rotate with respect to each other; (*d*) compound **17** 'stabilizes' the dimer in the active state and cyclothiazide prevents the rotation of domains away from each other.

tion, however, to such a degree that it is blocked almost completely.[78–80] Biarylpropylsulfamide derivatives also influence desensitization but the question of whether or not they affect deactivation still remains open.[81]

Potentiators of AMPA receptors enhance the synaptic transmission, namely, increase the amplitude and duration of excitatory post-synaptic potentials or currents.[82] Of particular interest is their ability to enhance long-term potentiation. The effect of long-tern potentiation of synaptic responses arising upon high-frequency stimulation of presynaptic fibres is retained for several tens of minutes and is believed to be a physiological memory equivalent.[83, 84] The modulators enhance this effect and promote its formation even if the frequency and the number of stimuli inducing it are lower than they should normally be.[53, 85]

An important feature of the modulator action is that almost all of them show preference toward particular subunits of AMPA receptors and their flip/flop variants. Thus cyclothiazide **16** is 10 times more active in the case of flip variants than in the case of flop variants,[78] while conversely, aniracetam (**17**) is more efficient for flop variants than for flip variants;[80] compound **21** has 20–70 μmol litre^{-1} affinity for flop-variants and is 1.5–3.0 less active for flip variants;[51] binding tests have shown that the affinity of compound **19** is higher for the flip form of GluR3 than for the flop form [86] and is three times higher for the flop variant of GluR2 than for the flop variants of the other three subunits (determined in electrophysiological experiments with recombinant AMPA receptors in the *Xenopus laevis* oocytes).[87] Biarylpropylsulfamide derivatives **26** and **27** potentiate AMPA receptors with homomeric GluR2 and GluR4 subunits more efficiently than with GluR1 and GluR3 subunits and potentiate flip variants more efficiently than flop variants.[88]

The results obtained to date imply that the known positive modulators of AMPA receptors are highly selective with respect to these receptors. For example, aniracetam does not potentiate kainate receptors.[89, 90] In the tests on binding of tritium-labelled kainate, compounds **21**, **19** (in concentrations of 1 mmol litre^{-1}) and **18** (5 mmol litre^{-1}) had no effect on binding.[65] Aniracetam did not affect the currents of native NMDA receptors;[56, 91] neither compound **19** (400 μmol litre^{-1}) nor compound **18** (1 mmol litre^{-1}) had an effect on the currents of recombinant NMDA receptors.[85] Compound **18** in a concentration of 2 mmol litre^{-1} had only a slight effect on binding to NMDA receptors and no effect on glutamate inclusion into synaptoneurosomes;[65] when present in 1 mmol litre^{-1} concentration, it did not change the monosynaptic inhibitory postsynaptic currents and, hence, had no effect on the γ-aminobutyric acid (GABA) receptors.[60] It was reported [92] that aniracetam acts on the metabotropic glutamate receptors in micromolar concentrations but in later studies, it was shown that this action is most likely due to the influence of its metabolite, *N*-anisoyl-GABA.[93] The effects of other positive modulators on the metabotropic glutamate receptors have not been studied.

AMPAkins are true modulators but not agonists as they do not themselves induce the currents (in any concentrations).[94] Biarylpropylsulfamides also do not affect other neuroreceptors; in particular, it was found that they have no influence on the GABA, kainate or NMDA receptors.[81]

Positive modulators of AMPA receptors are widely used to study the role of these receptors in the memory and cognitive mechanisms. These modulators enhance the response of AMPA receptors by decreasing their desensitization and/or deactivation. This improves the learning ability and memory, as was shown by the results of some behaviour tests on various animal species. The use of positive modulators provided higher learning ability of rats in a water [95] or radial maze,[96, 97] in odour discrimination tests,[98, 99] active avoidance tests [100] and in more complex conditioning tests.[101, 102]

Thus, positive modulators of AMPA receptors improve the learning ability and many kinds of memory. These modulators do not improve the verbal memory in humans but they proved to be efficient in many learning tasks.[103] These aspects of modulator action are the subjects of several recent reviews.[8, 55, 94, 104]

Modulators have a series of useful and important properties, which are manifested as a rule irrespective of the particular mechanism of modulator action. The crucial factor is the ability of the compound to potentiate the AMPA receptor responses confirmed in a number of experiments.

For example, positive modulators enhance the synthesis of the brain-derived neurotrophic factor (BDNF). It was shown [105] that four positive modulators of AMPA receptors, compounds **16**, **21**, **25** and **27**, with different mechanisms of action on the kinetics of AMPA receptors showed the neuroprotective effect on brain lesion in five-day-old mice caused by ibotenate, an NMDA receptor agonist. The action of any of the modulators was accompanied by enhancement of BDNF synthesis in hippocampus and cortex. This neuroprotector effect was implemented through mitogen-activated protein kinase (MAPK), as joint injection of a positive modulator and the MEK inhibitor PD-98059 (MEK is a MAPK activator) blocked the neuroprotective effect (Fig. 6).[12, 106] Thus it was shown that,

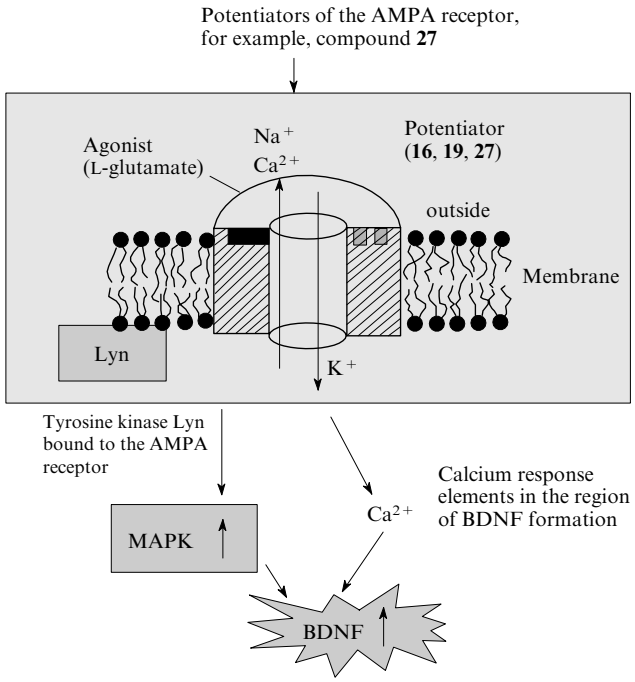


Figure 6. Metabolic routes to the synthesis of neurotrophic factors (BDNF) upon positive allosteric modulation of AMPA receptors.[11] Two possible routes are shown: Lyn-kinase-dependent route implemented through the MAPK system and the route related to increase in the calcium ion current through potential-activated calcium channels and AMPA receptors.

apart from the effect on ionotropic AMPA receptors, resulting in an increase in the transmembrane current, positive modulators also trigger a number of intracellular signalling systems and MAPK.[107, 108] Mitogen-activated protein kinase plays a highly important role in the mechanisms of intracellular protection of neurons from the external damaging factors.[109]

Apart from MEK activation, another way of increasing neurotrophic factors upon the action of positive modulators of AMPA receptors is also possible. It is related to the enhanced ingress of calcium ions into a neuron through both the ion channels of AMPA receptors (which do not contain GluR2 subunits) and the potential-activated calcium channels. As the calcium content inside the cell increases, the calcium-dependent site on the BDNF gene promoter is activated and triggers the alternative synthetic route to BDNF.[110] This is proven, in particular, by the following experiment: AMPAkin **21** increased in a dose-dependent manner the level of matrix RNA of BDNF. The increase in this level was blocked by AMPA receptor antagonists and L-type calcium channel antagonists. Besides the increase in the BDNF level, a short-term increase in the amount of matrix RNA of the nerve growth factor (NGF), also possessing a strong neuroprotective action, was also observed.[105]

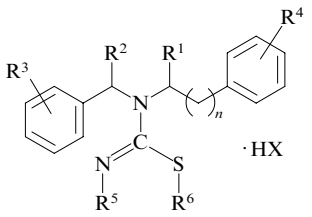
Moreover, upon subcutaneous administration, potentiators of AMPA receptors **27** and **28** cause a dose-dependent increase in the level of cyclic guanosine monophosphate (cGMP) in the rat cerebellum. This increase was specific, as it was completely blocked by the non-competitive antagonist of AMPA receptors, GYKI-53655. In addition, it was blocked by the non-competitive antagonist of NMDA receptor ion channel, MK-801, in amounts of 0.3 and 1.0 mg kg^{-1} (intraperitoneal administration); therefore, it is assumed that the increase in the cGMP level depends on activation of NMDA receptors. These results imply that an increase in cGMP can also play an important role in the pharmacological action of AMPA receptor potentiators.[111]

The synthesis of BDNF and NGF neurotrophic factors and the effect of other factors on neuron metabolism enhance considerably the therapeutic potential of the positive modulators of AMPA receptors. Recently they have been intensely studied on various models of neurodegenerative diseases with the aim of subsequent use for prevention and treatment of Alzheimer's and Parkinson's diseases and mental depression, which are typically accompanied by a decrease in the production of new neurons.[6, 9–12]

In view of neuroprotective properties of positive modulators of AMPA receptors, one can suggest that they should also have gerontoprotective effect. This was confirmed in chronic experiments *in vivo* with old animals.[112] Positive modulators were also shown to be effective in preventing neuron death in old animals in *in vitro* experiments.[113]

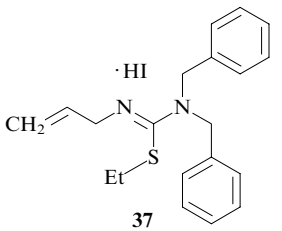
Preclinical and pilot clinical trials of a number of potentiators of AMPA receptors such as **18**, **26** and **27** showed their efficiency in improving the cognitive functions and memory in various behaviour tests and in treatment of a number of diseases.[5, 7, 8, 96]

A new class of positive modulators of AMPA receptors based on derivatives of acyclic isothioureas with the general formula

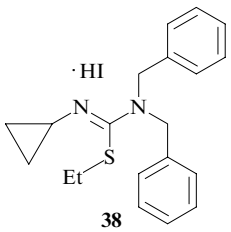


R^1, R^2 = H, Me; R^3, R^4 = Hal, Alk, OAlk; R^5 = Ar, Alk, cyclo-Alk; R^6 = Alk; X = Hal; n = 0, 1.

was synthesized at the Institute of Physiologically Active Compounds of the RAS.[114–118] The most active compounds of this class are 3-allyl-1,1-dibenzyl-2-ethylisothiourea hydroiodide (**37**) and 1,1-dibenzyl-3-cyclopropyl-2-ethylisothiourea hydroiodide (**38**). Being present in concentrations of 30 μmol $litre^{-1}$, they potentiated the currents of AMPA receptors to up to 1000% with respect to the conrol level.



37



38

The subsequent extended testing in animals confirmed the promising pharmacological profile of these compounds, which allows considering them as candidate drugs for treating Alzheimer's disease and cognitive enhancers.[119–121]

Analysis of the data presented in this review allows one to reasonably hope that further works on the synthesis and structure optimization of positive modulators of AMPA receptors would give rise in the near future to new-generation therapeutic agents for treating a broad range of neurodegenerative and psychoneurological diseases and to original memory and cognitive enhancers based on this class of physiologically active compounds.

The authors are sincerely grateful to B V Lednev for participation in preparing this review for publication.

References

1. J C Watkins, R H Evans *Ann. Rev. Pharmacol. Toxicol.* **21** 165 (1981)
2. J N C Kew, J A Kemp *Psychopharmacology (Berlin)* **179** 4 (2005)
3. J P Pin, T Galvez, L Prezeau *Pharmacol. Ther.* **98** 325 (2003)
4. R Dingledine, K Borges, D Bowie, S F Traynelis *Pharmacol. Rev.* **51** 7 (1999)
5. D C Goff, L Leahy, I Berman, T Posever, L Herz, A C Leon, S A Johnson, G J Lynch *Clin. Psychopharmacol.* **21** 484 (2001)
6. W Danysz *Curr. Opin. Investig. Drugs* **3** 1062 (2002)
7. T K Murray, K Whalley, C S Robinson, M A Ward, C A Hicks, D Lodge, J L Vandergriff, P Baumbarger, E Siuda, M Gates, A M Ogden, P Skolnick, D M Zimmerman, E S Nisenbaum, D Bleakman, M J O'Neill *J. Pharmacol. Exp. Ther.* **306** 752 (2003)
8. G Lynch, C M Gall *Trends Neurosci.* **29** 10 3 (2006)
9. M J O'Neill, J M Witkin *Curr. Drug Targets* **8** 603 (2007)
10. D Bleakman, A Alt, J M Witkin *CNS Neurol. Disord.–Drug Targets* **6** 117 (2007)

11. M J O'Neill, D Bleakman, D M Zimmerman, E S Nisenbaum *Curr. Drug Targets – CNS Neurol. Disord.* **3** 181 (2004)
12. M J O'Neill, T K Murray, K Whalley, M A Ward, C A Hicks, S Woodhouse, D J Osborne, P Skolnick *Eur. J. Pharmacol.* **486** 163 (2004)
13. G Lynch *Curr. Opin. Pharmacol.* **4** 4 (2004)
14. M Hollman, S Heinemann *Annu. Rev. Neurosci.* **17** 31 (1994)
15. C Rosenmund, Y Stern-Bach, C F Stevens *Science* **280** 1596 (1998)
16. P Francotte, P de Tullio, P Fraikin, S Counerotte, E Goffin, B Pirotte *Recent Pat. CNS Drug Discov.* **1** 239 (2006)
17. C Villmann, C-M Becker *Neurosci.* **13** 594 (2007)
18. J R Geiger, T Melcher, D S Koh, B Sakmann, P H Seeburg, P Jonas, H Monyer *Neuron* **15** 193 (1995)
19. D Bowie, M L Mayer *Neuron* **15** 453 (1995)
20. Y Sun, R Olson, M Horning, N Armstrong, M Mayer, E Gouaux *Nature (London)* **417** 245 (2002)
21. B Sommer, K Keinanen, T A Verdoorn, W Wisden, N Burnashev, A Herb, M Kohler, T Takagi, B Sakmann, P H Seeburg *Science* **249** 1580 (1990)
22. H Monyer, P H Seeburg, W Wisden *Neuron* **6** 799 (1991)
23. G T Swanson, S K Kamboj, S G Cull-Candy *J. Neurosci.* **17** 58 (1997)
24. P H Seeburg, J Hartner *Curr. Opin. Neurobiol.* **13** 279 (2003)
25. T B Stensbol, U Madsen, P Krogsgaard-Larsen *Curr. Pharm. Des.* **8** 857 (2002)
26. M L Mayer, N Armstrong *Annu. Rev. Physiol.* **66** 161 (2004)
27. J Drejer, T Honore *Neurosci. Lett.* **87** 104 (1988)
28. P J Birch, C J Grossman, A G Hayes *Eur. J. Pharmacol.* **156** 177 (1988)
29. M J Sheardown, E O Nielsen, A J Hansen, P Jacobsen, T Honore *Science* **247** 571 (1990)
30. J Ohmori, S Sakamoto, H Kubota, M Shimizu-Sasamata, M Okada, S Kawasaki, K Hidaka, J Togami, T Furuya, K Murase *J. Med. Chem.* **37** 467 (1994)
31. A Kohara, M Okada, R Tsutsumi, K Ohno, M Takahashi, M Shimizu-Sasamata, J Shishikura, H Inami, S Sakamoto, T Yamaguchi *J. Pharm. Pharmacol.* **50** 795 (1998)
32. L Turski, A Huth, M Sheardown, F McDonald, R Neuhaus, H H Schneider, U Dirnagl, F Wiegand, P Jacobsen, E Ottow *Proc. Natl. Acad. Sci. USA* **95** 10960 (1998)
33. M Takahashi, A Kohara, J Shishikura, S Kawasaki-Yatsugi, J W Ni, S Yatsugi, S Sakamoto, M Okada, M Shimizu-Sasamata, T Yamaguchi *CNS Drug Rev.* **8** 337 (2002)
34. S Solyom, I Tarnawa *Curr. Pharm. Des.* **8** 913 (2002)
35. J Ruel, M J Guitton, J-L Puel *CNS Drug Rev.* **8** 235 (2002)
36. D Bleakman, B A Ballyk, D D Schoepp, A J Palmer, C P Bath, E F Sharpe, M L Wooley, H W Bufton, R K Kamboj, I Tarnawa, D Lodge *Neuropharmacology* **35** 1689 (1996)
37. T Szabados, G Gigler, I Gacsalyi, I Gyertyan, G Levay *Brain Res. Bull.* **55** 387 (2001)
38. A S Chappell, J W Sander, M J Brodie, D Chadwick, A Lledo, D Zhang, J Bjerke, G M Kiesler, S Arroyo *Neurology* **58** 1680 (2002)
39. Y M Langan, R Lucas, H Jewell, N Toublanc, H Schaefer, J W A S Sander, P N Patsalos *Epilepsia* **44** 46 (2003)
40. B L Chenard, F S Menniti, M J Pagnozzi, K D Shenk, F E Ewing, W M Welch *Bioorg. Med. Chem. Lett.* **10** 1203 (2000)
41. W M Welch, F E Ewing, J Huang, F S Menniti, M J Pagnozzi, K Kelly, P A Seymour, V Guanowsky, S Guhan, M R Guinn, D Critchett, J Lazzaro, A H Ganong, K M DeVries, T L Staigers, B L Chenard *Bioorg. Med. Chem. Lett.* **11** 177 (2001)
42. F S Menniti, B L Chenard, M B Collins, M F Ducat, M L Elliott, F E Ewing, J I Huang, K A Kelly, J T Lazzaro, M J Pagnozzi, J L Weeks, W M Welch, W F White *Mol. Pharmacol.* **58** 1310 (2000)
43. J T Lazzaro, A V Paternain, J Lerma, B L Chenard, F E Ewing, J Huang, W M Welch, A H Ganong, F S Menniti *Neuropharmacology* **42** 143 (2002)
44. P Ascher, L Nowak *J. Physiol.* **399** 227 (1988)
45. J Mosbacher, R Schoepfer, H Monyer, N Burnashev, P Seeburg, J P Ruppersberg *Science* **266** 1059 (1994)
46. H Lomeli, J Mosbacher, T Melcher, T Hoger, J R P Geiger, T Kuner, H Monyer, M Higuchi, A Bach, P H Seeburg *Science* **266** 1709 (1994)
47. K M Partin *J. Neurosci.* **21** 1939 (2001)
48. I G Tikhonova, M I Lavrov, V A Palyulin, N S Zefirov *Dokl. Akad. Nauk* **399** 268 (2004) [a]
49. T Nakagawa, Y Cheng, E Ramm, M Sheng, T Walz *Nature (London)* **433** 545 (2005)
50. R Jin, S Clark, A M Weeks, J T Dudman, E Gouaux, K M Partin *J. Neurosci.* **25** 9027 (2005)
51. A C Arai, M Kessler, G Rogers, G Lynch *Mol. Pharmacol.* **58** 802 (2000)
52. N Nagarajan, C Quast, A R Boxall, M Shahid, C Rosenmund *Neuropharmacology* **41** 650 (2001)
53. U Staubli, G Rogers, G Lynch *Proc. Natl. Acad. Sci. USA* **91** 777 (1994)
54. U Staubli, Y Perez, F B Xu, G Rogers, M Ingvar, S Stone-Elander, G Lynch *Proc. Natl. Acad. Sci. USA* **91** 11158 (1994)
55. M J O'Neill, S Dix *IDrugs* **10** 185 (2007)
56. I Ito, S Tanabe, A Kohda, H Sugiyama *J. Physiol.* **424** 533 (1990)
57. K A Yamada, S M Rothman *J. Physiol.* **458** 409 (1992)
58. K A Yamada, C-M Tang *J. Neurosci.* **13** 3904 (1993)
59. A Guenzi, M Zanetti *J. Chromatogr.* **530** 397 (1990)
60. A Arai, M Kessler, G Rogers, G Lynch *J. Pharmacol. Exp. Ther.* **278** 627 (1996)
61. A C Arai, M Kessler, Y-F Xia, D Phillips, R Chamberlin, R Granger, G Lynch *Mol. Pharmacol.* **62** 566 (2002)
62. W Danysz *Curr. Opin. Investig. Drugs* **3** 1081 (2002)
63. M Bertolino, M Baraldi, C Parenti, D Braghiroli, M DiBella, S Vicini, E Costa *Recept. Chan.* **1** 267 (1993)
64. K A Yamada, M W Hill, Y Hu, D F Covey *Neurobiol. Dis.* **5** 196 (1998)
65. A C Arai, Y -F Xia, G Rogers, G Lynch, M Kessler *J. Pharmacol. Exp. Ther.* **303** 1075 (2002)
66. P Desos, B Serkiz, P Morain, J Lepagnol, A A Cordi *Bioorg. Med. Chem. Lett.* **6** 3003 (1996)
67. P L Ornstein, D M Zimmerman, M B Arnold, T J Bleisch, B Cantrell, R Simon, H Zarrinmayeh, S R Baker, M Gates, J P Tizzano, D Bleakman, A Mandelzys, K R Jarvie, K Ho, M Deverill, R K Kamboj *J. Med. Chem.* **43** 4354 (2000)
68. T A Shepherd, J A Aikins, D Bleakman, B E Cantrell, J P Rearick, R L Simon, E C Smith, G A Stephenson, D M Zimmerman, A Mandelzys, K R Jarvie, K Ho, M Deverill, R K Kamboj *J. Med. Chem.* **45** 2101 (2002)
69. P Miu, K R Jarvie, V Radhakrishnan, M R Gates, A Ogden, P L Ornstein, H Zarrinmayeh, K Ho, D Peters, J Grabell, A Gupta, D M Zimmerman, D Bleakman *Neuropharmacology* **40** 976 (2001)
70. H Zarrinmayeh, D Bleakman, M Gates, H Yu, D M Zimmerman, P L Ornstein, T McKennon, M B Arnold, W J Wheeler, P Skolnick *J. Med. Chem.* **44** 302 (2001)
71. J C Quirk, E S Nisenbaum *CNS Drug Rev.* **8** 255 (2002)
72. H Zarrinmayeh, E Tromiczak, D M Zimmerman, N Rankl, K H Ho, E Dominguez, A Castaño, A Escribano, C Fernandez, A Jimenez, W J Hornback, E S Nisenbaum *Bioorg. Med. Chem. Lett.* **16** 5203 (2006)
73. M C Fernandez, A Castano, E Dominguez, A Escribano, D Jiang, A Jimenez, E Hong, W J Hornback, E S Nisenbaum, N Rankl, E Tromiczak, G Vaught, H Zarrinmayeh, D M Zimmerman *Bioorg. Med. Chem. Lett.* **16** 5057 (2006)
74. M Sekiguchi, M W Fleck, M L Mayer, J Takeo, Y Chiba, S Yamashita, K Wada *J. Neurosci.* **17** 5760 (1997)
75. M Sekiguchi, K Yamada, J Jin, M Hachitanda, Y Murata, S Namura, S Kamichi, I Kimura, K Wada *NeuroReport* **12** 2947 (2001)
76. M Sekiguchi, K Nishikawa, S Aoki, K Wada *Br. J. Pharmacol.* **136** 1033 (2002)
77. M Kessler, A C Arai *Brain Res.* **1076** 25 (2006)
78. K M Partin, D K Patneau, M Mayer *Mol. Pharmacol.* **46** 129 (1994)

79. K M Partin, D Bowie, M L Mayer *Neuron* **14** 833 (1995)
80. K M Partin, M W Fleck, M L Mayer *J. Neurosci.* **16** 6634 (1996)
81. M Gates, A Ogden, D Bleakman *Neuropharmacology* **40** 984 (2001)
82. F Asztely, B Gustafsson *Mol. Neurobiol.* **12** 1 (1996)
83. T V P Bliss, G L Collingridge *Nature (London)* **361** 31 (1993)
84. S Maren, M Baudry *Neurobiol. Learn. Mem.* **63** 1 (1995)
85. A C Arai, Y-F Xia, E Suzuki *Neurosci.* **123** 1011 (2004)
86. Y F Xia, M Kessler, A C Arai *J. Pharmacol. Exp. Ther.* **313** 277 (2005)
87. J D Leever, S Clark, A M Weeks, K M Partin *Mol. Pharmacol.* **64** 5 (2003)
88. J C Quirk, E S Nisenbaum *J. Neurosci.* **23** 10953 (2003)
89. T H Johansen, A Chaudhary, T A Verdoorn *Mol. Pharmacol.* **48** 946 (1995)
90. J Lerma, A V Paternain, J R Naranjo, B Mellstrom *Proc. Natl. Acad. Sci. USA* **90** 11688 (1993)
91. P Xiao, M Staubli, M Kessler, G Lynch *Hippocampus* **1** 373 (1991)
92. M Pizzi, O Consolandi, M Memo, P Spano *Eur. J. Pharmacol.* **275** 311 (1995)
93. M Shirane, K Nakamura *Neuropharmacology* **39** 866 (2000)
94. A C Arai, M Kessler *Curr. Drug Targets* **8** 583 (2007)
95. I Zivkovic, D M Thompson, M Bertolino, D Uzunov, M DiBella, E Costa, A Guidotti *J. Pharmacol.* **272** 300 (1995)
96. C M Davis, B Moskovitz, M A Nguyen, B B Tran, A Arai, G Lynch, R Granger *Psychopharmacology* **133** 161 (1997)
97. R Granger, U Staubli, M Davis, Y Perez, L Nilsson, G A Rogers, G Lynch *Synapse* **15** 326 (1993)
98. J Larson, T Lieu, V Petchpradub, B LeDuc, H Ngo, G Rogers, G Lynch *J. Neurosci.* **15** 8023 (1995)
99. U Staubli, Z Izrael, F B Xu *Behav. Neurosci.* **110** 1067 (1996)
100. M T Rogan, U V Staubli, J E LeDoux *J. Neurosci.* **17** 5928 (1997)
101. R E Hampson, G Rogers, G Lynch, S A Deadwyler *J. Neurosci.* **18** 2740 (1998)
102. R E Hampson, G Rogers, G Lynch, S A Deadwyler *J. Neurosci.* **18** 2748 (1998)
103. M Ingvar, J Ambros-Ingerson, M Davis, R Granger, M Kessler, G A Rogers, R S Schehr, G Lynch *Exp. Neurol.* **146** 2 553 (1997)
104. K S Raevskii, K O Eremin *Biomed. Khim.* **50** 6 523 (2004) [b]
105. J C Lauterborn, G Lynch, P Vanderklish, A Arai, C Gall *J. Neurosci.* **20** 8 (2000)
106. E Dicou, C M Rangon, F Guimiot, M Spedding, P Gressens *Brain Res.* **970** 221 (2003)
107. Y Wang, J P Durkin *J. Biol. Chem.* **270** 22783 (1995)
108. M S Perkinton, T S Sihra, R J Williams *J. Neurosci.* **19** 5861 (1999)
109. P T Kotzbauer, P A Lampe, R O Heuckeroth, J P Golden, D J Creedon, E M Johnson Jr, J Milbrandt *Nature (London)* **384** 467 (1996)
110. T Hayashi, H Umemori, M Mishina, T Yamamoto *Nature (London)* **397** 72 (1999)
111. J W Ryder, J F Falcone, J R Manro, K A Svensson, K M Merchant *J. Pharmacol. Exp., Ther.* **319** 1 293 (2006)
112. S O Bachurin, V V Grigoriev, E Ph Shevtsova, I V Koroleva, L G Dubova, E G Kireeva *Exp. Gerontol.* **42** 142 (2007)
113. E B Bloss, R G Hunter, E M Waters, C Munoz, K Bernard, B S McEwen *Exp. Neurol.* **210** 1 109 (2008)
114. S O Bachurin, V V Grigoriev, O A Drany, A N Proshin, S E Tkachenko *J. Neurochem.* **73** S143D (1999)
115. S Bachurin, S Tkachenko, I Baskin, N Lermontova, T Mukhina, L Petrova, A Ustinov, A Proshin, V Grigoriev, N Lukoyanov, V Palyulin, N Zefirov *Ann. N.Y. Acad. Sci.* **939** 219 (2001)
116. RF P. 2223952 (2004); *Byull. FIPS* (5) (2004)
117. RF P. 2252936 (2005); *Byull. FIPS* (15) (2005)
118. V V Grigoriev, S O Bachurin, A N Proshin, V A Palulin, N S Zefirov, in *Procceedings of the 7th International Conference 'Alzheimer's and Parkinson's Diseases', Sorento, Italy, 2005* R. 95
119. N N Lermontova, T V Mukhina, G I Van'kin, T P Serkova, S O Bachurin *Byull. Eksp. Biol. Med.* **135** 1 58 (2003) [c]
120. S O Bachurin, V V Grigor'ev, T A Ivanova, E A Kustova, A N Proshin, in *Sovremennoe Sostoyanie Issledovanii, Diagnostiki i Terapii Neirodegenerativnykh Zabolevanii (Bolezni Al'tsgeimera, Parkinsona i dr.), Moskva, 2005* [Current State of Investigations, Diagnostics and Therapy of Neurodegenerative Diseases (Alzheimer's, Parkinson's Diseases, *etc.*), Moscow, 2005] p. 99
121. B K Beznosko, V V Grigor'ev, T A Ivanova, I V Koroleva, M I Lavrov, A N Proshin, S O Bachurin *Psikhofarmakol. Biol. Narkol.* **7** 1604 (2007)

[a] — *Dokl. Biochem. Biophys. (Engl. Transl.)*
[b] — *Biomed. Chem. (Engl. Transl.)*
[c] — *Bull. Exp. Biol. Med. (Engl. Transl.)*