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ORIGINAL PAPER

Ab Initio studies of receptor interactions with AMPA ((*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid) and Kainic acid (2S-(2α,3β,4β))-2-carboxy-4-(1-methylethenyl)-3-pyrrolidineacetic acid

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Abstract The optimum geometries and binding energies of the complexes formed by AMPA and Kainic acid, as well as their anions with tyrosine, proline and some tripeptides are investigated with quantum chemical calculations (HF/6-31G**). It was found that receptors featuring the Tyr-Ala-Pro sequence exhibit stronger binding energies to the substrates than the Tyr-Ser-Pro and Tyr-Ser-Ser. As expected, the anions are more bound than the neutral species. This work can lead to investigations on the effect of AMPA receptors mutations on the brain functions, possibly related to criminal tendencies.

Keywords AMPA · Hartree-fock · Kainic acid · Receptor

Introduction

Disorders of brain functions can lead to serious behavioral problems [1, 2], among which could be the committing of crimes [3]. This area of study is called Forensic Psychology and uses expertise with human motivation and pathology to contribute to criminal investigations.

Such personality disorders as paranoia, schizophrenia, obsession-compulsion and others can play a major role in the criminal behavior. Since the AMPA ((*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid) receptors and their misfunction can lead to mental disorders, it might be of interest to study in more details the binding between these receptors and some of their ligands, such as AMPA and Kainic acid.

AMPA receptors (AMPARs) play an essential role in the mammalian brain, regulating fast excitatory synaptic transmission. The insertion of additional AMPARS which are glutamate-gated ion channels, into synapses after short periods of high-frequency activity, produces a strengthening of synaptic transmission related to processes of learning and memory [4].

Beside AMPA receptors, ionotropic glutamate receptors feature *N*-methyl-*D*-Aspartic (NMDA) receptors and Kainic acid (KA) receptors. These three subclasses are based on their binding affinities for their respective agonist ligands. They play an important role also in neuronal degeneration associated with cerebral ischemia, Parkinson's disease and Alzheimer's disease [5–7].

As shown by Pentikainen et al. [8], two sequence positions Arg 485 and Glu705 in AMPA, NMDA and KA receptors, play a key role in ligand binding. Accordingly, they apply molecular modeling studies, using Protein Data Bank to dock the ligands into their respective receptors.

The receptors contain also tyrosine and proline residues. The present work applies *ab initio* (Hartree-Fock) calculations to the study of the interaction between AMPA and tyrosine or AMPA and proline. In addition, interactions between tyrosine or proline and Kainic acid are also studied.

Pentikainen et al. [8] indicates the presence of a Tyr-Ala-Pro sequence in the AMPAr. The equivalent sequence in the Kainic acid receptor is Tyr-Ser-Ser. To investigate interactions between such sequences and their respective ligands, the present work uses *ab initio* (Hartree-Fock)

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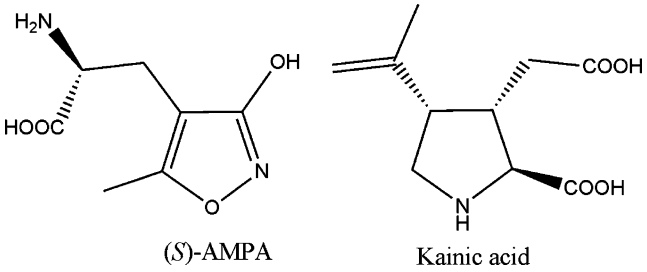

Fig. 1 Structure of the ligands considered in this study

calculations. Two kinds of systems are investigated: the complexes formed by AMPA and Kainic acid as well as their anionic forms with proline and tyrosine and the complexes formed by AMPA and Kainic acid and their anions with the three peptides Tyr-Ala-Pro, Tyr-Ser-Pro, and Tyr-Ser-Ser. Indeed, the last two might represent pathological mutations taking place in the receptors, leading to different mental disorders, possibly criminal tendencies.

Methods and results

The calculations are performed using the Hartree-Fock method, with the 6–31G** basis set, as implemented by the Spartan program [9]. The 6–31G** basis set is known to provide a good description of molecular systems. The optimized systems are minima, since there are no negative eigenvalues. The binding energies of the complexes are calculated by subtracting the sum of the energies of the subsystems from the total energy of the complex. The solvation energies [10] are calculated in the same way. The method is based on AM1 calculations Fig. 1.

Table 1 shows the binding energies of AMPA and Kainic Acid, as well as their ions to tyrosine and proline. Table 2 shows the binding energies of AMPA, Kainic Acid and their ions to the Tyr-Ala-Pro, Tyr-Ser-Pro and Tyr-Ser-Ser tripeptides.

Table 1 Binding energies of AMPA and Kainic Acid complexes with proline and tyrosine

Compound	ΔE (kcal mol^{-1})	ΔE (solvation, kcal mol^{-1})
2	−8.0	1.1
3	−10.2	2.9
4	−18.4	−3.7
5	−30.6	8.7
6	−2.3	2.1
7	−4.3	3.3
8	−11.4	1.3
9	−26.4	6.7
10	−23.0	18.0
11	−38.7	11.8

Table 2 Binding energies of AMPA, Kainic acid and their aions with the peptides

Compound	ΔE (kcal mol^{-1})	ΔE (solvation, kcal mol^{-1})
12	−7.3	3.9
13	−13.9	6.7
14	−11.3	16.0
15	−29.9	31.8
16	−26.2	22.3
17	−29.3	21.3
18	−9.8	8.9
19	–	11.3
20	−7.9	17.1
21	−26.5	7.4
22	–	15.1
23	−43.1	27.0
24	−58.4	5.4
25	−15.2	12.3
26	−50.9	21.5

Figures 2–5 show the complexes formed by AMPA with proline (Fig. 2) and with tyrosine (Fig. 3), by the AMPA anion with proline (Fig. 4) and with tyrosine (Fig. 5). Figures 6–11 show the complex formed by Kainic acid with proline (Fig. 6), and with tyrosine (Fig. 7), the complex formed by the kainate anion with proline (Fig. 8) and with tyrosine (Fig. 9), the complex formed by the kainate dianion with proline (Fig. 10) and with tyrosine (Fig. 11).

Figures 12, 13 and 14 show the complexes formed by AMPA with Tyr-Ala-Pro.

Tyr-Ser-Pro and Tyr-Ser-Ser respectively. Figures 15, 16 and 17 show the complexes formed by the AMPA anion with the three peptides.

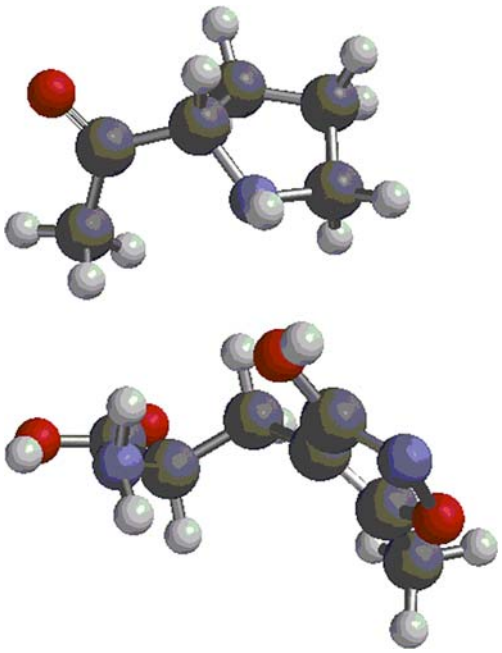

Fig. 2 Complex formed by AMPA with proline

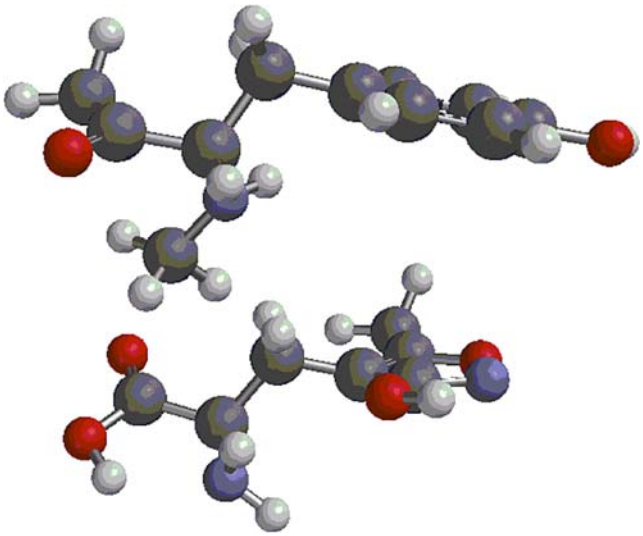

Fig. 3 Complex formed by AMPA with tyrosine

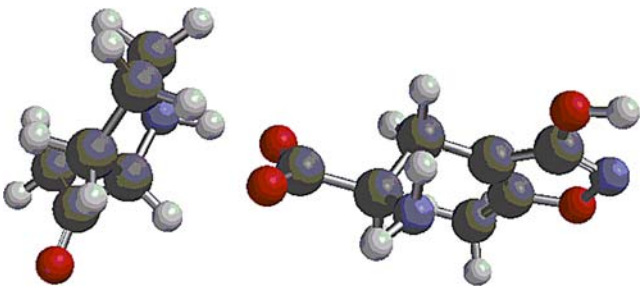

Fig. 4 Complex formed by the AMPA anion with praline

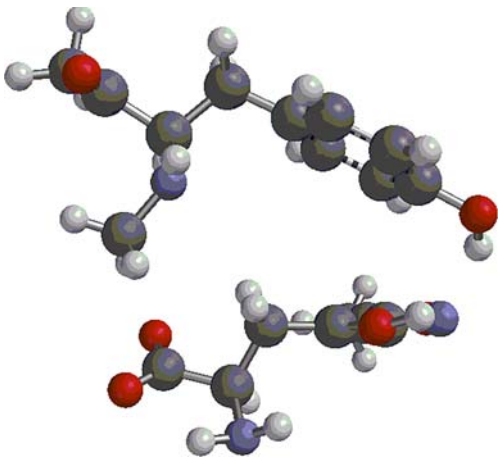

Fig. 5 Complex formed by the AMPA anion with tyrosine

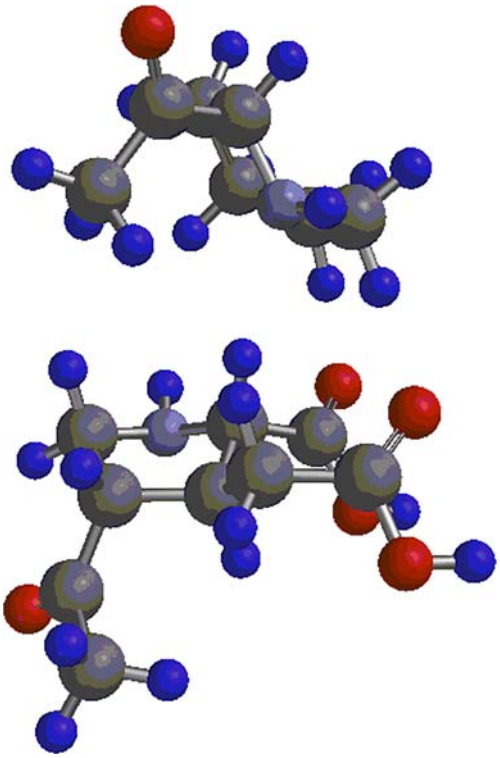

Fig. 6 Complex formed by Kainic acid with proline

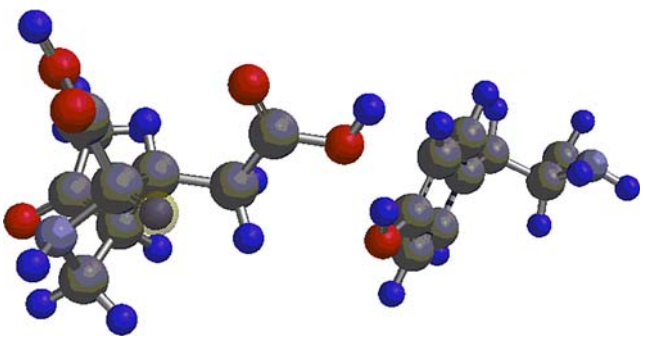

Fig. 7 Complex formed by Kainic acid with tyrosine

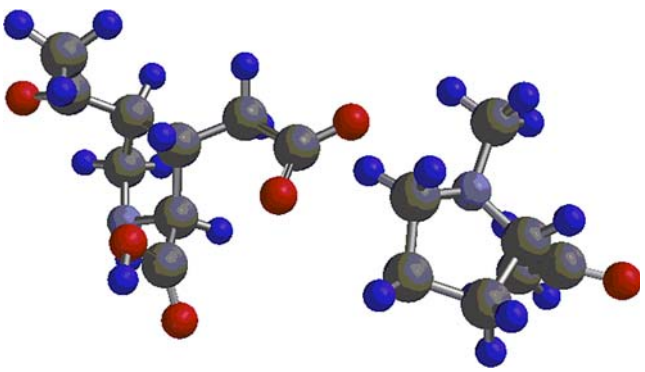

Fig. 8 Complex formed by the kainate anion with proline

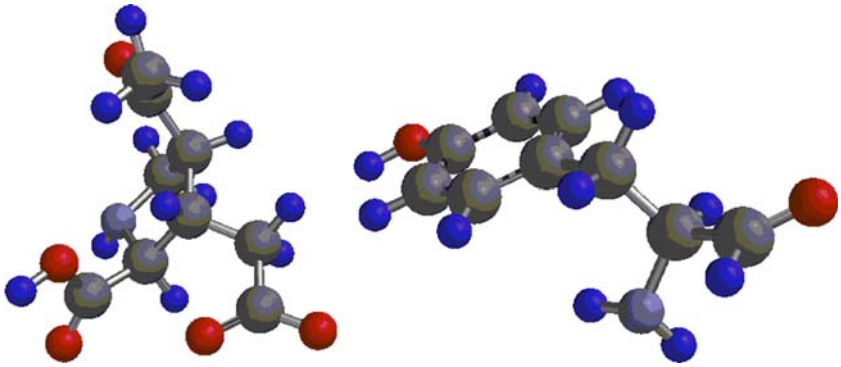

Fig. 9 Complex formed by the kainate anion with tyrosine

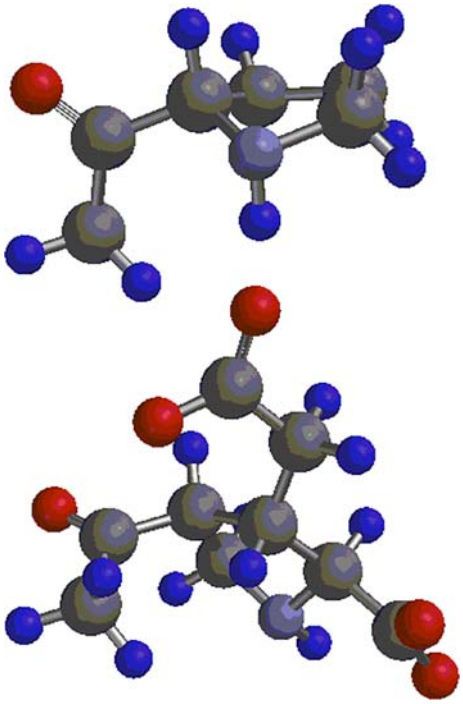

Fig. 10 Complex formed by the kainate dianion with proline

Figures 18, 19 and 20 show the complexes formed by Kainic acid with the three peptides while Figures 21, 22, 23, 24, 25, 26 show the complexes formed by the kainate anion and the kainate dianion with the three peptides.

Tables 1 and 2 show also the binding solvation energies of all the complexes, calculated as the solvation energy of the complex minus the sum of the solvation energies of the subsystems.

Discussion

Colona et al. [11] and Pentikainen et al. [8] report that the AMPA receptor features the presence of such residues as tyrosine, proline, serine, and alanine. Accordingly, the complexes of AMPA and Kainic acid with proline and tyrosine were examined, in order to calculate their binding energies. As seen from Table 1, AMPA features a stronger binding energy than Kainic acid, to both amino acids. The binding to tyrosine is stronger than the binding to proline, if the solvation energy is not taken into account. Otherwise, they become similar. If at the pH present in the system AMPA and Kainic acid are ionized, the binding energy

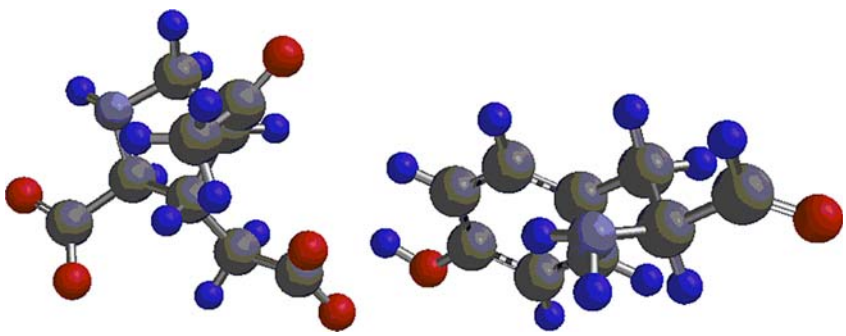

Fig. 11 Complex formed by the kainate dianion with tyrosine

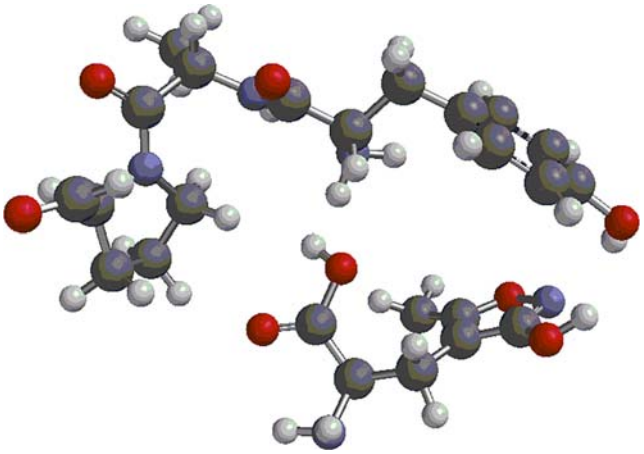

Fig. 12 Complex formed by AMPA with Tyr-Ala-Pro

becomes much higher, especially for the dianion of Kainic acid with tyrosine, which features a binding energy of −38.7 kcal mol^{-1}. If the positive difference in solvation energy is added, still the system is left with −27.9 kcal mol^{-1} binding energy. The binding in these complexes occurs mostly *via* hydrogen bonding. It is easy to understand that the anions binding stronger than the neutral species, since the attraction between strongly negative oxygens and positively charged hydrogens is strong. Indeed, the oxygens in the carboxyl group of the AMPA and Kainate feature charges about −.9 e and some hydrogens in proline and tyrosine feature charges from .5 to .8 e. The charges were calculated by the Natural Population Analysis method.

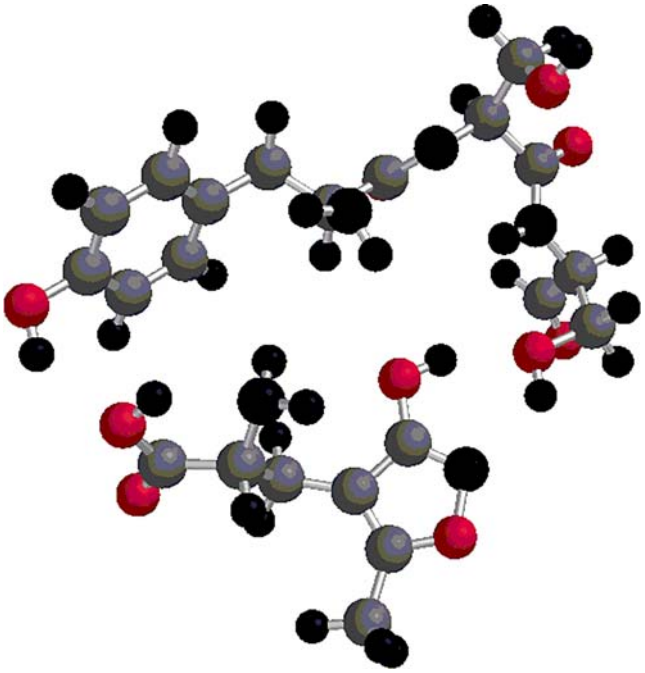

Fig. 14 Complex formed by AMPA with Tyr-Ser-Ser

As far as the complexes formed by the tripeptides with AMPA, Kainic Acid and their anions are concerned, it can be seen from Table 2, that Kainic acid and its monoanion are not bound to the Tyr-Ser-Pro peptide. Only the dianion kainate shows a binding energy of −15.2 kcal mol^{-1}, much smaller than its binding energy to Tyr-Ala-Pro (−58.4 kcal mol^{-1}) and Tyr-Ser-Ser (−50.9 kcal mol^{-1}). Kainic acid and its monoanion are also bound to these two peptides, as shown in Table 2. However, if the binding solvation energy is taken into consideration, Kainic acid is not bound to Tyr-Ser-Ser.

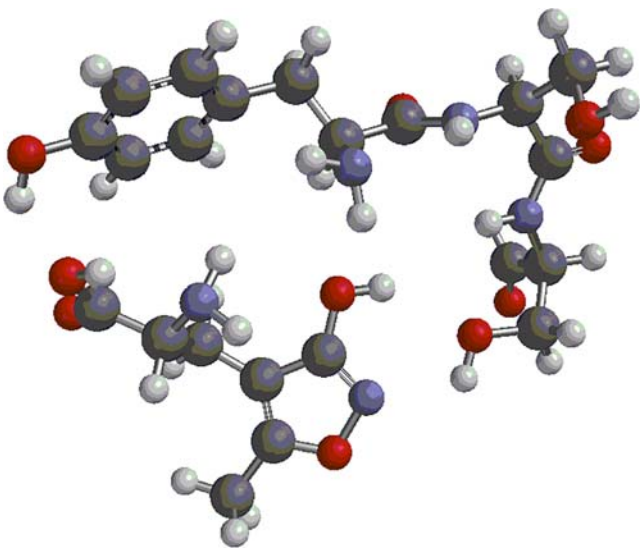

Fig. 13 Complex formed by AMPA with Tyr-Ser-Pro

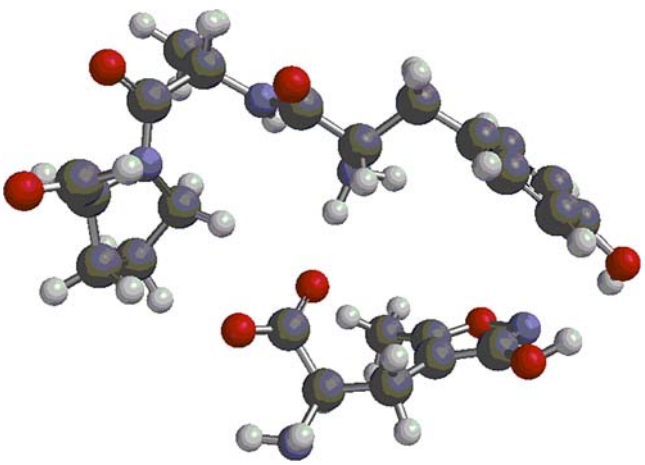

Fig. 15 Complex formed by the AMPA anion with Tyr-Ala-Pro

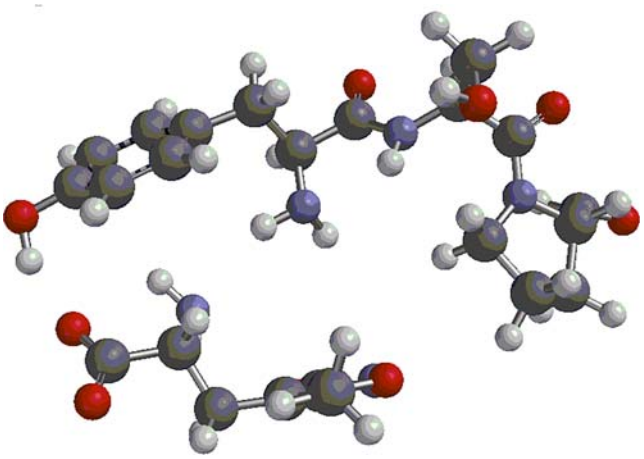

Fig. 16 Complex formed by the AMPA anion with Tyr-Ser-Pro

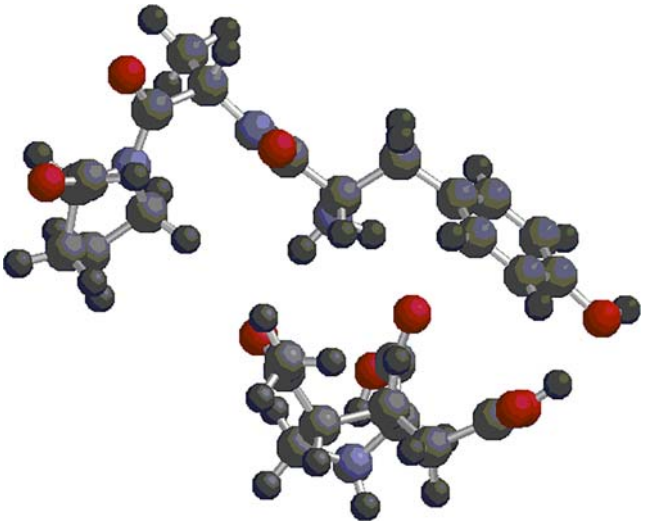

Fig. 18 Complex formed by Kainic acid with Tyr-Ala-Pro

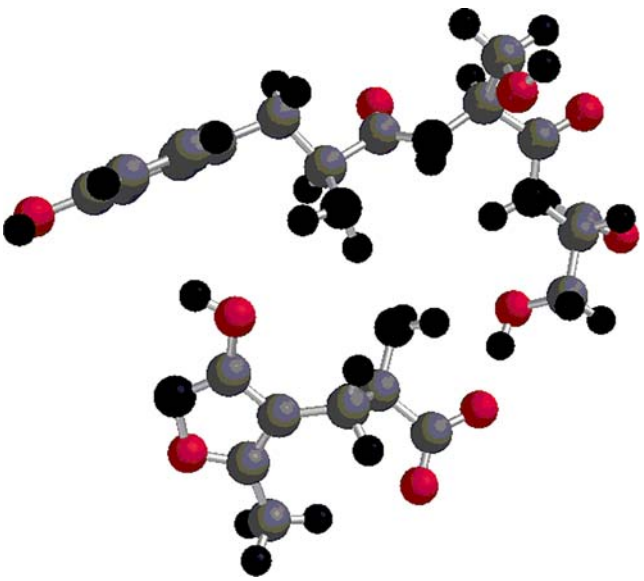

Fig. 17 Complex formed by the AMPA anion with Tyr-Ser-Ser

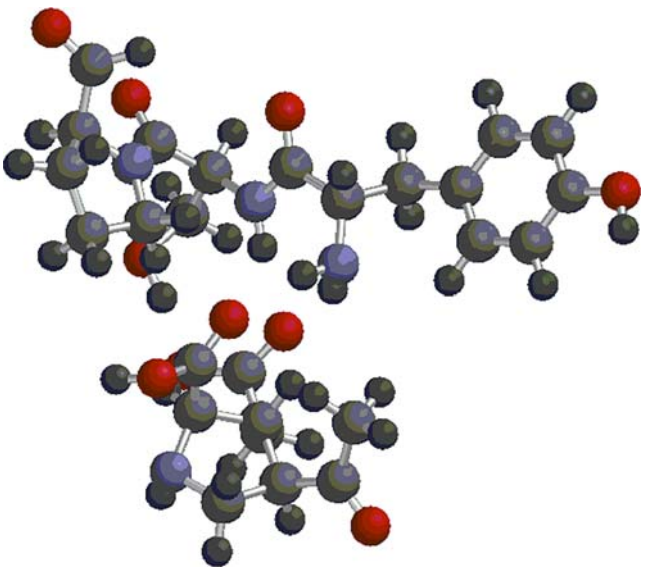

Fig. 19 Complex formed by Kainic acid with Tyr-Ser-Pro

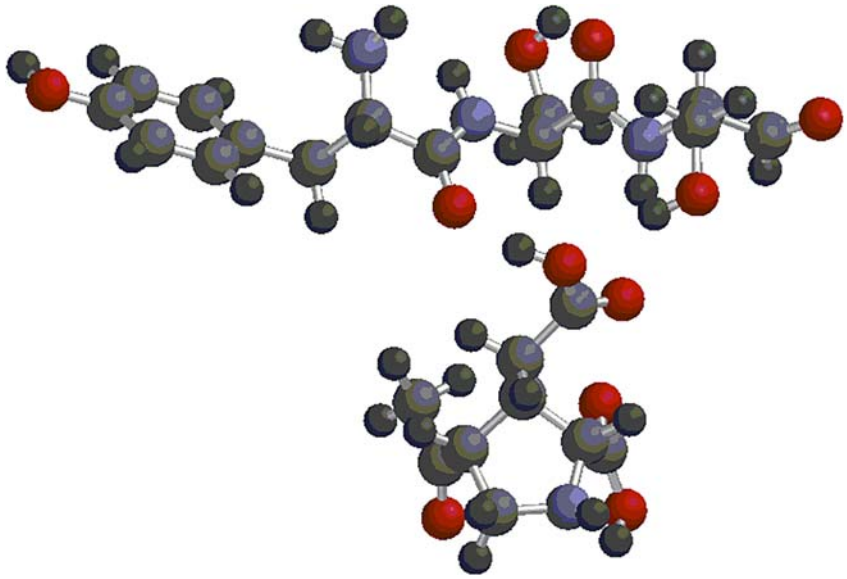

Fig. 20 Complex formed by Kainic acid with Tyr-Ser-Ser

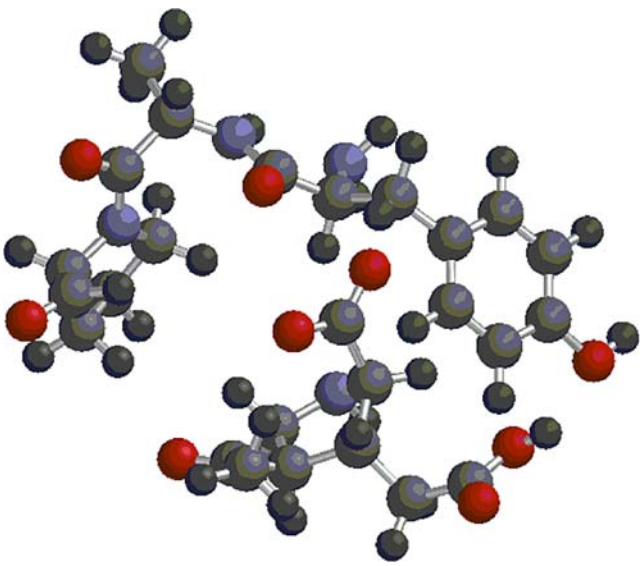

Fig. 21 Complex formed by the kainate anion Tyr-Ala-Pro

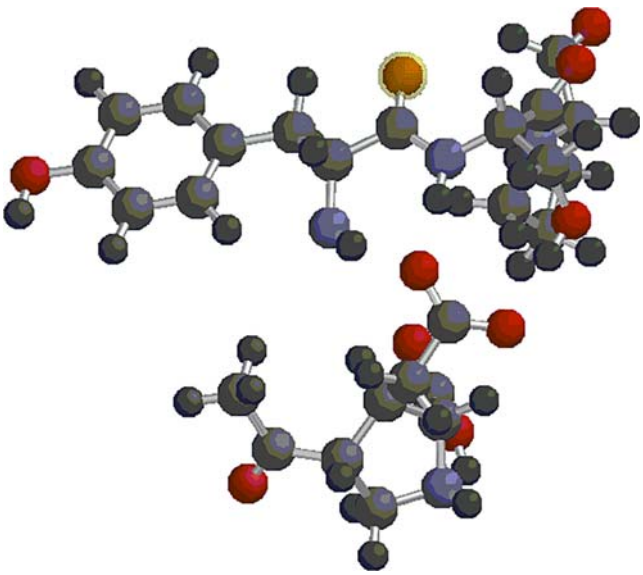

Fig. 22 Complex formed by the kainate anion Tyr-Ser-Pro

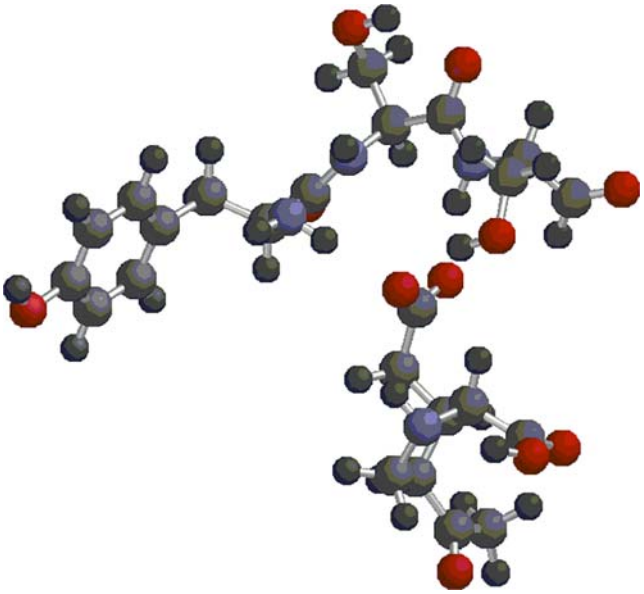

Fig. 23 Complex formed by the kainate anion Tyr-Ser-Ser

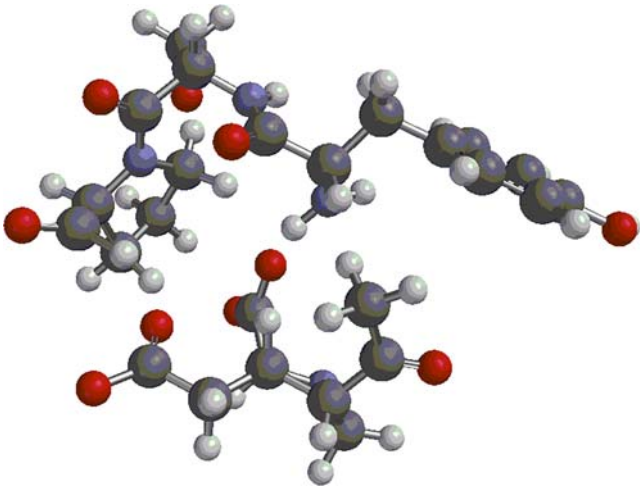

Fig. 25 Complex formed by the kainate dianion Tyr-Ser-Pro

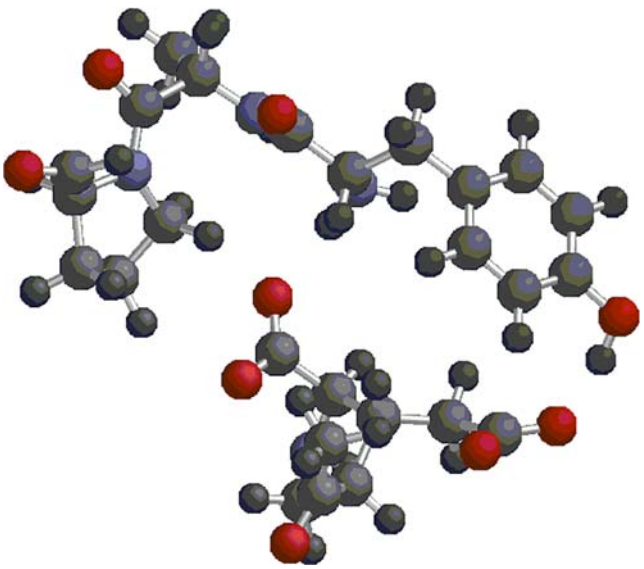

Fig. 24 Complex formed by the kainate dianion Tyr-Ala-Pro

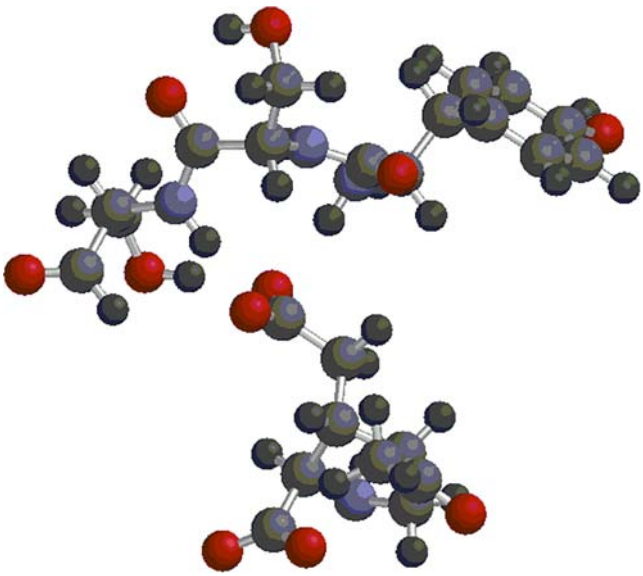

Fig. 26 Complex formed by the kainate dianion Tyr-Ser-Ser

These results show that eventual mutations occurring in the AMPA receptors in the brain can lead to significant differences in the binding of the substrates. It is possible that these modifications influence some processes in the brain, such as learning disabilities, memory issues and criminal tendencies. Experimental studies of the correlation between mutations in the AMPA receptors and personality changes such as aggressive behavior in animals might shed a light on these issues.

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