

**The development of novel anti-depressant targeting AMPA receptor**Hara Megumi*Yokohamacity university*

Depression is the major mental disorder characterized by the decrease of motivation, interest and activity and over one million patients are suffering from this disease. It was also reported that the number of patients showing resistance toward anti-depressant, i.g. SSRI and SNRI, got increase nowadays. We have already known that molecular mechanism underlying depression is heterogeneous so that it is hard to estimate the efficacy of anti-depressant depends without molecular rationale. Postmortem human brain analysis indicated that the number of AMPA receptors (AMPARs), major molecule controlling synaptic functions, varied among depression patients compared to healthy subjects and these results were not consistent. To clarify the dynamics of AMPARs in depression patients, we developed the PET (positron emission tomography) imaging drug to measure the density of AMPARs in depression patients. This result showed that depression patient decreased AMPARs expression broadly throughout the brain. This fact motivated us to develop novel AMPARs potentiator in order to cure the depression. To find the compound showing high affinity to AMPARs and high BBB penetrability, we modified the compound A, previously known to bind specifically to and activate AMPARs, and finally succeeded in synthesizing the seed compound B, showing higher BBB penetrability compared with compound A. This compound B could exert the anti-depressant effect quickly and sustained for a week after withdrawal from repetitive one-week administration. Furthermore, this anti-depressant effect was significantly stronger than another AMPARs potentiators already under development in clinical trials.