Speaker 2: Yasumasa Okamoto
Title: The role of serotonin in waiting for future rewards in depression
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Abstract
Serotonin (5-HT) is a major neuromodulator implicated in a broad assortment of behavioral and physiological functions, including aggression, appetite, aversion, behavioral inhibition and impulsivity. The 5-HT system is one of the most important targets for the treatment of depression. It has been difficult, however, to explain the diverse effects of serotonin on adaptive behavior within a unified framework. Based on the review of experimental data and theoretical models, we previously proposed a model in which the function of serotonin is to modulate the value of waiting for a future reward. In this hypothesis, a higher level of 5-HT means a higher setting of the discount factor, which promotes waiting for longer delays. A low level of serotonin is often associated with impulsive behaviors (Doya, 2002). Here, we show a part of the results of a series of research carried out based on the hypothesis.

Human functional magnetic resonance imaging (fMRI) studies show differential involvement of brain areas in the prediction of immediate and delayed rewards, with the dorsal striatum and prefrontal cortex showing consistent activity for delayed rewards (Tanaka et al., 2004). To elucidate the role of serotonin in the evaluation of delayed rewards, we performed an fMRI experiment in which subjects chose either small-immediate or large-delayed rewards under dietary regulation of tryptophan, a precursor of serotonin. The study showed that the dorsal striatal activity correlated with long-term reward prediction was enhanced with the activation of the serotonergic system (Tanaka et al., 2007). From the behavioral data, we found an increase of proportion in small reward choices, together with an increase in the rate of discounting of delayed rewards in the low-serotonin condition compared with the control and high-serotonin conditions (Schweighofer et al., 2008). Recently, we found the attenuated activation in the dorsal striatum during waiting for delayed rewards in depressed patients (Okada et al., in preparation).

To examine any causal relationship between serotonergic activity and waiting behavior for delayed reward, we applied a 5-HT₁₆ receptor agonist locally in the dorsal raphe nucleus (DRN) in rats; this treatment is known to suppress 5-HT neural activity through autoreceptors. Rats performed a sequential food-water navigation task in which they alternately visited food and water sites to acquire rewards after waiting periods. The rats performed the task under two reward conditions: a short delayed reward condition and a long delayed reward condition. We found that the suppression of 5-HT neural activity in the DRN by a 5-HT₁₆ receptor agonist increased premature exit from reward sites before the delivery of delayed rewards, which indicated impaired patience for delayed rewards (Miyazaki et al., 2012).

From both human and animal studies, these results strongly supported our hypothesis that 5-HT promotes waiting for longer delays, and might explain not only impulsive behavior, but also certain aspects of depressive behavior.

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Speaker 3: Zaida Diaz-Cabiale
Title: Galanin and galanin fragment 1–15 modulate antidepressant responses by targeting 5-HT1A-GalR heteroreceptor complexes of the ascending midbrain serotonin pathways
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Abstract
Mood disorders, including depression and anxiety, are among the most prevalent mental illnesses with high socioeconomic impact. Although the underlying mechanisms have not yet been clearly defined in the last decade the importance of the role of neuropeptides, including Galanin (GAL), and/or their receptors in the treatment of stress-related mood disorders is becoming increasingly apparent.

From both human and animal studies, these results strongly supported our hypothesis that 5-HT promotes waiting for longer delays, and might explain not only impulsive behavior, but also certain aspects of depressive behavior.

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Doya K. Metalearning and neuromodulation. Neural Netw. 2002; 15: 495–506.
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Schweighofer N, Bertin M, Shishida K, Okamoto Y, Tanaka SC, Yamawaki S, Doya K. Low-serotonin levels increase delayed reward discounting in humans. J. Neurosci. 2008;28:4528–4532.
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GAL is involved in mood regulation, including depression-related and anxiety-like behaviors. Activation of GALR1 and GALR3 receptors results in a depression-like behavior while stimulation of GALR2 receptor leads to anti-depressant-like effects. Moreover, GAL modulates 5-HT1A receptors (5-HT1AR), a key receptor in depression at autoreceptor and postsynaptic level in the brain. This interaction can in part be due to the existence of GALR1-5-HT1AR heteroreceptor complexes in discrete brain regions [5]. Not only GAL but also the N-terminal fragments like GAL(1–15) are active in the Central Nervous System [2, 3]. Recently, we described that GAL(1–15) induces strong depression-related and anxiogenic-like effects in rats, and these effects were significantly stronger than the ones induced by GAL [4]. The GALR1-GALR2 heteroreceptor complexes in the dorsal hippocampus and especially in the dorsal raphe (DR), areas rich in GAL(1–15) binding sites [5], were involved in these effects [4, 6] and demonstrated also in cellular models.

In the present study, we have analyzed the ability of GAL(1–15) to modulate 5-HT1AR located at postjunctional sites and at the soma-dendritic level in rats. We have analyzed the effect of GAL(1–15) on the 5-HT1AR-mediated response in a behavioral test of depression and the involvement of the GALR2 in these effects. GAL(1–15) enhanced the antidepressant effects induced by the 5-HT1AR agonist 8-OH-DPAT in the forced swimming test [7]. These effects were stronger than the ones induced by GAL. The mechanism of this action involved interactions at the receptor level in the plasma membrane with changes also at the transcriptional level. Thus, GAL(1–15) affected the binding characteristics as well as the mRNA level of 5-HT1AR in the dorsal hippocampus and DR. GALR2 was involved in these effects, since the specific GALR2 antagonist M871 blocked GAL(1–15) mediated actions at the behavioral and receptor level [7].

Furthermore, the results on the proximity ligation assay (PLA) in this work suggest the existence of GALR1-GALR2-5-HT1AR heteroreceptor complexes since positive PLA were obtained for both GALR1-5-HT1AR and GALR2-5-HT1AR complexes in the DR and hippocampus. Moreover, the studies on RN33B cells, where GALR1, GALR2 and 5-HT1AR exist [4], also showed PLA-positive clusters indicating the existence of GALR1-5-HT1AR and GALR2-5-HT1AR complexes in these cells [7].

In conclusion, our results indicate that GAL(1–15) enhances the antidepressant effects induced by the 5-HT1AR agonist 8-OH-DPAT probably acting on GALR1-GALR2-5-HT1AR heteroreceptor located at postjunctional sites and at the soma-dendritic level. The development of new drugs specifically targeting these heteroreceptor complexes may offer a novel strategy for treatment of depression.

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S20: Finding Autism Before Diagnosis: identification of very early signs of autism spectrum disorders in human and mice

Chair: Noboru Hiroi, USA
Co-Chair: Jae Won Kim, Republic of Korea

Speaker 1: Katarzyna Chawarska, USA
Title: Attentional signature of autism in infancy: Studies of siblings at risk for ASD