様式３

論　文　内　容　の　要　旨

氏　名　（　佐藤彰典　）	
論文題名	セロトニンの視覚刺激検出能に対する修飾作用とその神経基盤 （Modulatory effects of serotonin on perceptual visual detectability of rat and the underlying neuronal mechanism）

論文内容の要旨

The information processing in the brain dynamically changes depending on behavioral context, and psychological state. The dynamics are regulated mainly by neuromodulators such as serotonin (5-hydroxytryptamine; 5-HT), regulating various brain functions such as arousal, sleep, emotion, and memory.

Serotonergic neurons in raphe nucleus project their axons to the cerebral cortex including visual areas, modulating neural activities in the areas via various subtypes of 5-HT receptors. A previous study reported that 5-HT receptor-selective agonists facilitate or suppress visual responses in monkey primary visual cortex (V1), suggesting that serotonin may optimize visual information processing by the bidirectional effects (Watakabe et al., 2009). However, it remains unclear whether and how serotonin affects visual functions at perceptual level. To investigate this point, firstly, I measured contrast sensitivity (CS) of freely moving rats as an index of perceptual visual detectability using a two-alternative forced choice-visual detection task (2AFC-VDT) with drifting grating stimulus in combination with the staircase method. Fluoxetine (FLX), a selective serotonin reuptake inhibitor, or saline was intraperitoneally administered at 5 mg/kg 30 minutes before the task. FLX administration significantly improved CS only at grating spatial frequency (SF) of 0.1 but not 0.5 cycle/degree, suggesting that endogenous serotonin modulates perceptual visual detectability and the possible action site is V1 neurons showing specificity for SF of grating.

Next, to clarify the neural mechanism of the effect of serotonin on CS, I established a new visual stimulus detection task under head-fixed condition, which enables perceptual CS measurement and recordings of extracellular single-unit activity in V1 simultaneously. I tested the effect of Ketanserin, an antagonist of 5-HT2A receptor, on the CS and neural activities of V1 neurons using the task. Ketanserin was intravenously administered with 2 mg/kg via the tail vein of rats, improving significantly CS and facilitating the neuronal visual responses. It suggests that serotonin modulates visual perception via 5-HT2A receptor. However, it is not unclear whether and how much neuronal activity in V1 contributes to perceptual decision-making. Therefore, we compared visual responses between Hit and Miss trials for each neuron using a receiver operating characteristic analysis. Under control (no drug) condition, about 20% of V1 neurons were observed to be correlated to the task performance, and interestingly, the correlation was increased by ketanserin, suggesting that serotonin modulates not only cortical visual information processing but also contribution of visual signal in V1 to perceptual decision-making via 5-HT2A receptor.

This study showed that endogenous serotonin in the brain improves perceptual visual detectability, but decreases perceptual visual detectability via activation of 5-HT2A receptors alone. The discrepancy for serotonin actions can be explained by different subtypes of 5-HT receptors. In V1, at least, 5-HT2A and 1B receptors are present, and those have been known to act in an opposing way. Serotonin may improve visual detectability mainly via 5-HT1B receptor and may be balanced with 5-HT2A receptor.

In conclusion, serotonin released to V1 depending on behavioral context, such as rhythmical exercise, controls perceptual visual detectability by modulating neural activities bidirectionally in V1 and changing contribution of V1 activity to visual percept.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

神経修飾物質であるセロトニンは行動文脈応じて脳内情報処理を動的に調節している。これまで、神経活動レベルにおいてはセロトニンが一次視覚野の視覚応答を促通あるいは抑制するなど双方向性に修飾することが報告されていたが、知覚レベルにおける視覚機能への影響とその神経機序は明らかになっていなかった。

本博士研究では、ラットを用いた行動薬理実験を行い、脳内セロトニン濃度の上昇作用を持つセロトニン再取り込み阻害剤の投与が視覚刺激検出能を向上させることを見出した。また、視覚刺激検出能測定中にラット一次視覚野の神経活動記録を行い、セロトニン受容体の一種である5-HT2A受容体を拮抗阻害することで視覚刺激検出能の向上と一次視覚野神経応答の促通が引き起こされることを明らかにした。

これらの研究結果は、脳内のセロトニンが、5-HT2A受容体を介して一次視覚野神経応答を修飾し、知覚レベルにおいても視覚機能を調節していることを強く示唆するとともに、セロトニンの機能的役割について視知覚の点から新たな知見を与え、多岐にわたるセロトニンの機能解明に貢献することが期待される。

よって、佐藤彰典に博士の学位を授与するに相応しいと判断された。