- 1P186 ラット海馬 CA1 領域の上昇層、放射状層、網状分子層におけるエストロゲンによる神経細胞スパインへの効果
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Comparison between Basal and Apical Dendritic Spines in Estrogen-Induced Rapid Spinogenesis Principal Neurons in the rat Hippocampal CA1
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Modulation of hippocampal synaptic plasticity by estrogen has been attracting much attention. Here, we demonstrated the rapid effect of 17 β -estradiol on the density and morphology of spines which is thought to be significantly related with synaptic plasticity in the stratum oriens (s.o., basal side), stratum radiatum (s.r. apical side), and in the stratum lacunosummoleculare (s.l.m., apical side) by imaging Lucifer Yellow-injected CA1 neurons in adult male rat hippocampal slices. Spines in s.o. and s.l.m. have been poorly understood as compared with spines in the s.r. so far. The application of 1 nM estradiol-induced a rapid increase in the density of spines of pyramidal neurons within 2 h. In all regions ERa agonist PPT but not ERb agonist DPN induced the same enhancing effect of spinogenesis as that induced by estradiol. This increase by estradiol was blocked by estrogen receptor inhibitor ICI and Erk MAP kinase inhibitor PD98059 in all regions. Effect of blockade by agonists of AMPA receptors and NMDA receptors was different between basal and apical side. These results indicate that estradiol activate Erk MAP kinase cascade through ERa, and induce spinogenesis within 2 h in all regions, which need moderate calcium influx through NMDA receptor or AMPA receptor.

- 1P188 海馬樹状突起スパインに及ぼす男性ホルモンの急性的効果
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Androgens rapidly increased the density of spines in the hippocampus
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The hippocampus is a center for learning and memory. Dendritic spines are postsynaptic structures. It has been reported that the application of testosterone and dihydrotestosterone have anti-anxiotic effects. Therefore, the effects of androgens on hippocampal spine morphology has been attracting much attention. Androgens are known to change the synaptic plasticity of hippocampal neurons by modulating gene transcription, but its genomic actions are very slow. We demonstrated androgens rapidly affect the number and morphology of dendritic spines in rat dorsal hippocampus. Hippocampal slices were incubated with testosterone or dihydrotestosterone for another 2 hours. We observed that these androgens increased spine density from 0.98 (spines/ μ m) to 1.26 (spines/ μ m), especially for thin-type spine, which has a small head and functional membrane molecules. After washing out these androgens, the number of spines returned to control level. Because these changes of spine morphology and density are very rapid, and transcription inhibitor has no effect, it is suggested that those processes are mediated not by gene transcription but by membrane associated androgen receptor responses and its downstream signal transducers. We have uncovered that MAP kinase superfamily, such as ERK1/2 and p38 were involved in this signaling.

- 1P187 女性ホルモンによる海馬神経細胞スパインの形態変化
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Dynamics of synapses modulated by estradiol in hippocampus
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Single neuron has nearly 10,000 spines along about 40 dendrites. Spines are postsynaptic structures and they store memories in the hippocampus. We are demonstrating that steroid hormones are synthesized not only in the gonads but also locally in the brain hippocampus, and that these steroids act rapidly to modulate neuronal plasticity via synaptic receptors. The depletion of estrogen causes impairment of learning and memory, depression, anxiety, and increase in the risk of Alzheimer disease. We demonstrated that dendritic spines were rapidly modulated by estradiol application, by means of single spine analysis of Lucifer-Yellow injected neurons in adult male hippocampal slices. 3D images were obtained from confocal microscopic measurements. Following a 2 h treatment with estradiol in the stratum radiatum of CA1 region, the treated dendrites have significantly more spines at 1 nM estradiol (1.35 spines/ μ m) than control dendrites at 0 nM estradiol (0.94 spines/ μ m). To determine the downstream target of estrogen, we further examined the effect of various antagonists. Antagonist of estrogen receptor alpha and an inhibitor of ERK MAP kinase were both suppressed the effect of estrogen. The channel blocker of NMDA receptor also showed the same effect. These results indicate that estrogen acts via ER alpha and drives the ERK MAP kinase pathway, and that the cascade needs the spontaneously occurring calcium influx from the NMDA receptor.

- 1P189 ラット海馬における性ステロイドおよびストレスステロイドホルモンの合成
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Androgen and estrogen synthesis in the rat hippocampus
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It is widely accepted that dihydrotestosterone (DHT) and 17 β -estradiol (E2), the main androgen and estrogen in mammals, reaches the brain via blood circulation and modulate efficiency of learning and synaptic plasticity. However, recent study suggests the possibility that androgen and estrogen are synthesized in the rat brain as well as in gonads. This indicates that brain-derived androgen and estrogen act as a modulator of synaptic plasticity. DHT, E2 and their precursors and metabolites are synthesized by enzyme cytochrome P450(17 α), P450(arom), 3 β -HSD, and 17 β -HSD, but presence and activity of those enzymes in the rat brain are still unclear. To prove the presence of androgen and estrogen synthesis pathway, we examined the expression level of mRNA of those enzymes in adult male rat brain by means of the semi-quantitative RT-PCR. This experiment demonstrated the presence of the enzymes required corticosterone synthesis pathway in the brain and also determined the relative level of mRNA expression for those enzymes. We also measured the activity of those enzymes in rat hippocampal slices by means of the radiolabeled steroid metabolism assay. With tritium-labeled precursor steroids as substrate, we detected the activity of rat hippocampal slices synthesizing DHT and E2. These results indicate that the pathway of synthesis of androgen and estrogen exist in rat hippocampal neurons. We are also investigating the pathway of stress steroid synthesis in hippocampus.