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A106: Aerobic Exercise Modulates GPCR/cAMP/PKA Signaling Pathway and Complement-Microglia Axis to Prevent Synaptic Loss in APP/PS1 Mice

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A106: Aerobic Exercise Modulates GPCR/cAMP/PKA Signaling Pathway and Complement-Microglia Axis to Prevent Synaptic Loss in APP/PS1 Mice

Abstract

Purpose: Synaptic failure serves as a primary contributor to memory dysfunction in Alzheimer's disease (AD). Physical exercise has demonstrated the potential to thwart and delay degenerative alterations in memory functions linked to AD. Investigating the underlying mechanisms may unveil crucial insights into early pathological changes, offering breakthroughs for both understanding and treating AD. Methods: We utilized 3-month-old APP/PS1 mice and subjected them to a 12-week aerobic exercise intervention. The spatial learning and memory functions of the mice were assessed using the Morris water maze test, while Golgi staining was employed to determine dendritic spine density in each mouse group. To analyze the potential mechanisms mediating the effects of exercise intervention in the AD brain, we conducted RNA sequencing. Subsequently, pathway enrichment analysis, immunofluorescence, real-time quantitative PCR, and western blotting were employed to elucidate the impact of regular aerobic exercise on the GPCR/cAMP/PKA signaling pathway and complement-microglia axis. Results: Our findings reveal that a 12-week aerobic exercise intervention significantly enhanced spatial learning and memory function in APP/PS1 mice. Moreover, it led to a substantial increase in dendritic spine density and elevated expression of postsynaptic density protein 95 (PSD-95) in the cortex and hippocampus. Aerobic exercise demonstrated the ability to improve the expression of certain genes and enhance synaptic pathways in the brains of APP/PS1 mice. This suggests that aerobic exercise facilitates synaptic growth in APP/PS1 mice by modulating G protein-coupled receptors (GPCRs) and activating the cAMP signaling pathway, with significant alterations observed in the expressions of Hcar1 and Vipr2 genes. Furthermore, exercise intervention resulted in the significant down-regulation ($P < 0.05$ or $P < 0.01$) of cAMP, p-PKA/PKA, GluA1, and CaMKII protein expressions in the brain tissue of APP/PS1 mice, which were subsequently up-regulated after exercise ($P < 0.01$). Notably, regular aerobic exercise effectively suppressed the activation of IBA-1+ microglia cells ($P < 0.01$), reversed changes in M1 phenotype markers (Cd86 and iNOS) and M2 phenotype markers (Arg-1) of microglia cells ($P < 0.05$), reduced the production of promoters C1q and central factor C3 in the macrosomatic cascade ($P < 0.05$), and prevented the colocalization of microglia and PSD-95 ($P < 0.01$). Conclusion: In conclusion, our results indicate that physical exercise plays a pivotal role in fostering early synaptic growth and averting synaptic loss in Alzheimer's disease (AD). This effect may be attributed to the regulation of the G protein-coupled receptors (GPCRs)/cAMP/PKA signaling pathway and the suppression of complement-mediated microglial phagocytosis of synapses. This mechanistic insight underscores the inherent contribution of exercise to health promotion, offering potential avenues for synaptic-focused interventions in the early stages of AD treatment.

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Purpose: Synaptic failure serves as a primary contributor to memory dysfunction in Alzheimer's disease (AD). Physical exercise has demonstrated the potential to thwart and delay degenerative alterations in memory functions linked to AD. Investigating the underlying mechanisms may unveil crucial insights into early pathological changes, offering breakthroughs for both understanding and treating AD. **Methods:** We utilized 3-month-old APP/PS1 mice and subjected them to a 12-week aerobic exercise intervention. The spatial learning and memory functions of the mice were assessed using the Morris water maze test, while Golgi staining was employed to determine dendritic spine density in each mouse group. To analyze the potential mechanisms mediating the effects of exercise intervention in the AD brain, we conducted RNA sequencing. Subsequently, pathway enrichment analysis, immunofluorescence, real-time quantitative PCR, and western blotting were employed to elucidate the impact of regular aerobic exercise on the GPCR/cAMP/PKA signaling pathway and complement-microglia axis. **Results:** Our findings reveal that a 12-week aerobic exercise intervention significantly enhanced spatial learning and memory function in APP/PS1 mice. Moreover, it led to a substantial increase in dendritic spine density and elevated expression of postsynaptic density protein 95 (PSD-95) in the cortex and hippocampus. Aerobic exercise demonstrated the ability to improve the expression of certain genes and enhance synaptic pathways in the brains of APP/PS1 mice. This suggests that aerobic exercise facilitates synaptic growth in APP/PS1 mice by modulating G protein-coupled receptors (GPCRs) and activating the cAMP signaling pathway, with significant alterations observed in the expressions of Hcar1 and Vipr2 genes. Furthermore, exercise intervention resulted in the significant down-regulation ($P<0.05$ or $P<0.01$) of cAMP, p-PKA/PKA, GluA1, and CaMKII protein expressions in the brain tissue of APP/PS1 mice, which were subsequently up-regulated after exercise ($P<0.01$). Notably, regular aerobic exercise effectively suppressed the activation of IBA-1+ microglia cells ($P<0.01$), reversed changes in M1 phenotype markers (Cd86 and iNOS) and M2 phenotype markers (Arg-1) of microglia cells ($P<0.05$), reduced the production of promoters C1q and central factor C3 in the macrosomatic cascade ($P<0.05$), and prevented the colocalization of microglia and PSD-95 ($P<0.01$). **Conclusion:** In conclusion, our results indicate that physical exercise plays a pivotal role in fostering early synaptic growth and averting synaptic loss in Alzheimer's disease (AD). This effect may be attributed to the regulation of the G protein-coupled receptors (GPCRs)/cAMP/PKA signaling pathway and the suppression of complement-mediated microglial phagocytosis of synapses. This mechanistic insight underscores the inherent contribution of exercise to health promotion, offering potential avenues for synaptic-focused interventions in the early stages of AD treatment.