

Action of Neurosteroid Pregnenolone in the Brain

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神經類固醇 P5 對腦子的功能

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Steroids have been widely used in treating inflammation, hormonal imbalance and disorder of reproduction. They are popular drugs because of their small size and the ease of administration. A new class of steroids, neurosteroids, has recently gained interest because of their roles in the brain. Pregnenolone (abbreviated as P5) in neuronal tissues improves memory and cognition and helps neurological recovery. In addition, it is required for zebrafish embryonic epiboly migration and microtubule abundance. However, the detail mechanism of P5 functions is unknown. Here we explore the possibility of using zebrafish as a model to study the action of P5. We showed that P5 decreases zebrafish anxiety and increases learning/memory in behavior tests. We also showed that P5 promotes cell migration and microtubule polymerization by binding to a microtubule plus end protein Cytoplamic Linker Protein 1 (CLIP-170). We captured CLIP-170 from zebrafish embryonic extract using a P5 photoaffinity probe linked to diaminobenzophenone. Upon binding P5, CLIP-170 became more extended, increased its interaction with p150^{Glued} and LIS1, and promoted microtubule polymerization more efficiently. CLIP-170 was essential for P5 to promote epiboly migration, and over-expression of P5-binding domain CLIP-170₈₉₀₋₉₉₀ in zebrafish embryos caused epiboly delay. P5 was also required for microtubule growth and the directional migration of mouse adrenocortical Y1 cell. Our results elucidate the mechanism of P5 action in promoting cell migration and microtubule polymerization. The interaction of P5 and CLIP-170 may be a therapeutic target for the treatment of memory loss, or neurodegenerative or psychiatric disorders.