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Synaptic plasticity is altered by supraphysiological levels of retinoic acid acting nongenomically however endogenous retinoic acid has not been shown to control synaptic plasticity

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Abstract

A paper recently published on forebrain cortical synaptic plasticity reports that retinoic acid (RA) induces synaptopodin-dependent metaplasticity in mouse dentate granule cells (Lenz et al., 2021). Retinoic acid (RA) is the active form of vitamin A that functions as a ligand for nuclear RA receptors that directly bind genomic control regions to regulate gene expression (Chambon, 1996; Ghyselinck and Duester, 2019). However, Lenz et al. report that RA functions in a nongenomic fashion to control forebrain cortical synaptic plasticity which modulates synaptic transmission to effectively respond to specific stimuli; specifically, they report that this nongenomic response occurs in the dorsal hippocampus but not ventral hippocampus. They performed RA treatment studies which provided information on how a supraphysiological level of RA effects synaptic plasticity. However, the authors did not perform an RA loss-of-function study to verify that endogenous RA is required for synaptic plasticity.

Supraphysiological Levels of RA Alter Synaptic Plasticity

The only method Lenz et al. used to determine RA function was to treat mice with 10 mg/kg RA. However this dose of RA results in micromolar concentrations of RA in mouse tissues which is a toxic or teratogenic dose (Nau, 1995); RA is normally present in the nanomolar range in brain and other tissues (Kurlandsky et al., 1995). Such high levels of RA cannot be used to determine the normal function of RA due to unwanted side-effects. In fact, one cannot determine the normal in vivo functions of RA by adding RA. Instead, one must take away RA preferably using RA genetic loss-of-function studies in vivo to be certain that RA is required for any proposed function (Cunningham and Duester, 2015).

The article in question here is one of a series of articles suggesting that RA controls synaptic plasticity in a nongenomic fashion using a mechanism that does not involve regulation of gene expression by nuclear RA receptors, but instead involves cytoplasmic RA receptors that control mRNA translation or perhaps other nongenomic processes (Aoto et al., 2008; Arendt et al., 2015;

Zhang et al., 2018; Hsu et al., 2019). However, Lenz et al. and these other articles did not perform a genetic loss-of-function study to remove endogenous RA to see if it is required for synaptic plasticity via any mechanism. In order to do this in brain is difficult as several enzymes may participate in RA synthesis. However, it has been possible to eliminate RA synthesis in mouse fetal brain using knockouts of the RA-generating enzymes encoded by *Aldh1a2* or *Aldh1a3* (Chatzi et al., 2011); RA production has also been successfully eliminated in adult mouse cornea using a triple conditional knockout of *Aldh1a1*, *Aldh1a2*, and *Aldh1a3* (Kumar et al., 2017). Although sometimes very difficult, genetic loss-of-function studies are needed to determine the function of any gene, protein, or in this case a molecule such as RA.

Summary

In order for the reader to be able to accept the conclusion that RA controls synaptic plasticity the authors would need to determine that endogenous RA is present, determine where in the adult brain and under what conditions RA is generated, and then genetically knockout RA-generating enzymes to remove endogenous RA and determine if this has an effect on synaptic plasticity. If so, then it would be relevant to determine whether the mechanism proceeds through nuclear RA receptors or in a nongenomic manner that involves cytoplasmic RA receptors or some other process. This is important as there currently are no RA genetic loss-of-function studies that support any nongenomic mechanism for RA. As it stands now, Lenz et al. have only told us that supraphysiological amounts of RA can alter synaptic plasticity in a nongenomic fashion.

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