Treatment of pregnant mice with valproic acid caused an increase in miR-132 levels in the embryonic brain.

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We have previously reported that mice prenatally exposed to valproic acid (VPA) at embryonic day 12.5 (E12.5) exhibit autism spectrum disorder (ASD)-like phenotypes. On the other hand, small non-coding RNAs known as microRNA (miRNA) have emerged as potential players in the pathology of neurodevelopmental disorders such as ASD. Here, we examined effects of prenatal VPA exposure on levels of miRNAs, especially the brain specific and enriched miRNAs, in the mouse embryonic brain. VPA exposure at E12.5 immediately increased miR-132 levels, but not miR-9 or miR-124 levels. The VPA exposure at E12.5 increased mRNA levels of Arc, c-Fos and BDNF prior to miR-132 expression. In contrast, VPA exposure at E14.5 did not affect miR-132 levels. The VPA exposure at E12.5 further decreased mRNA levels of MeCP2 and p250GAP, both of which are molecular targets of miR-132. Moreover, RNA sequence analysis revealed the VPA exposure-induced changes in several miRNA levels other than miR-132. These findings suggest that the alterations in neuronal activity-dependent miRNAs levels, including increased miR-132, in the embryonic period, at least in part, underlie the ASD-like phenotypes and cortical pathology in mice prenatally exposed to VPA.