Rett syndrome (RTT) is a progressive neurodevelopmental disorder mainly caused by mutations in the X-linked *MECP2* gene, which represents the main genetic cause of intellectual disability in girls worldwide. Since MeCP2 is highly expressed in mature neurons, the majority of studies are focused on this cell type. However, besides neurons, astrocytes have been identified as active contributors to RTT pathogenesis, as *Mecp2* knock-out (KO) astrocytes fail to correctly support neuronal maturation and synaptogenesis. Indeed, culturing wild-type (WT) neurons with KO astrocytes or treating them with KO astrocyte-conditioned medium (ACM) affects their synaptic phenotype. Of note, one of the key synaptogenic factors released by astrocytes is cholesterol, which plays a crucial role in synapse formation and functioning. Several data highlight a defective cholesterol metabolism in RTT, supporting the hypothesis that abnormalities in astrocyte-produced cholesterol might contribute to synaptic dysfunctions. In this study, we report a downregulation of genes involved in cholesterol synthesis and secretion in *Mecp2* KO astrocytes and an alteration in the activation of Srebp2, that represents the master regulator of cholesterol metabolism. In a therapeutic perspective, we found that Trofinetide, the only FDA-approved drug for RTT, attenuates in KO astrocytes the transcriptional defects of cholesterol-related genes, whereas cholesterol treatment completely rescues the synaptic alterations both in WT neurons treated with KO-ACM and *Mecp2* heterozygous (HET) neurons. To corroborate *in vitro* evidence, we moved to investigations in adult mouse models, proving a deregulation of key factors involved in cholesterol metabolism in the brain of Mecp2 deficient animals. Collectively, these data demonstrate an alteration of cerebral cholesterol metabolism in RTT and suggest cerebral cholesterol supply as a possible therapeutic strategy for repairing synaptic dysfunctions in RTT.