Long interspersed element-1 retrotransposition induced by valproic acid depends on NR2A

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The human genome consists of interspersed repeats, sequences that mark the long-standing activities and high preservative quality of mobile DNA. Long interspersed element-1 (*LINE-1* or *L1*), a highly active autonomous retrotransposon (RTP), is the most abundant endogenous retroelement in humans accounting for approximately 17% of the human genome, approximately 10% of which are "hot L1" copies primed for "jumping" within the genome. Recent studies have demonstrated the induction of L1 activity by drugs or low-molecular-weight compounds, but little is known about the underlying mechanism. The aim of this study was to identify the mechanism by which valproic acid induces L1-RTP. We found that valproic acid induced L1-RTP at a frequency of $\sim 10^4$, which was attributed to the nongenotoxic effects of the compound. Our results revealed that valproic acid induced L1-RTP in neuronal cell lines. Using inhibitors and siRNAs, we showed that NMDA receptor 2A (NR2A) was the first target of valproic acid. Interestingly, a biochemical analysis revealed that valproic acid induced L1-RTP in a NR2A receptor-dependent manner. Moreover, valproic acid activated MAPK via phosphorylated p44/42 MAPK, and PD98059 acted as a MAPK inhibitor to inhibit valproic acid-induced L1-RTP. Overall, L1-RTP induced by valproic acid is a novel type of genomic instability, and analysis of this phenomenon might be a novel approach to elucidate the mechanism of substance-use disorders.