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Oxytocin (OXT) is used on approximately 43% of women who give birth in the U.S. to induce or augment labor. The maximum OXT dose varies between women from ≤ 2mU/min to ≥ 20mU/min. Those requiring ≥ 20mU/min of OXT are defined as "high-dose requiring (HDR)." The biological cause underlying these individual differences in OXT response is unknown, however, maternal genetics is suspected to be a factor. Our laboratory has identified three variants (H173R, R150L, and R151C) in the oxytocin receptor (OXTR) gene in women who are HDR. H173R, R150L, and R151C were located in the binding and signaling domains of the OXTR and were predicted by SIFT ("Sorting Intolerant From Tolerant") algorithm to be damaging to protein function. Another variant, A218T, was identified in approximately 22% of HDR and LDR women but predicted to be non-damaging to protein function. We hypothesized that the variants found in HDR individuals and predicted to be damaging would attenuate OXTR signaling. OXTR variants were created via mutagenesis and transfected into HEK293T and hTERT cells. Monoclonal HEK293 cell lines stably expressing wild-type (WT) OXTR and R150L+A218T OXTR were generated. The OXTR signaling ability of the WT and variants was assessed with an ELISA assay using IP1 accumulation as the readout for OXTR signaling. Calcium imaging was also used to measure OXTR function.

WT OXTR were functional as measured by the ELISA and calcium imaging. Higher doses of OXT led to greater stimulation of the OXTR and greater IP1 accumulation in cells transfected with WT OXTR. Cells stably expressing R150L+A218T OXTR were found to produce less IP1 compared to the WT OXTR. Our studies show that genetic variants found in HDR individuals may attenuate OXTR signaling. If so, this may help improve clinical methods and treatments using OXT during labor and delivery.