Prematurely menopausal women have a doubled lifetime risk of dementia. The mechanisms underlying this phenomenon remain unclear, but prolonged loss of ovarian 17β-estradiol (E2) may play a key role. Previously, we noted that young female rats subjected to 10-week ovariectomy demonstrated a loss of E2 neuroprotection from global cerebral ischemia (GCI) and a decrease in expression of the estrogen receptor co-regulator Proline-, Glutamate-, and Leucine-Rich Protein 1 (PELP1). Thus, we hypothesized that neural E2 signaling may be altered following surgical menopause due to a decrease in PELP1 expression. To investigate, we ovariectomized 3-month-old female rats and immediately initiated low-dose, subcutaneous E2 therapy. One week following continuous treatment, animals were subjected to 10 min GCI, and hippocampi were harvested. We simultaneously knocked down PELP1 intracerebroventricularly with anti-sense oligonucleotides daily for 3 days prior to inducing ischemia. Missense oligos served as a control. In vivo knockdown of PELP1 reversed E2 neuroprotection status and negated E2's prevention of cJun N-terminal Kinase (JNK) activation and AD-related protein induction in the hippocampal CA1 region. Mass spectrometry and co-immunoprecipitation studies further identified JNK and its upstream signaling pathway members M KK7, MLK3, and POSH as potential PELP1-interacting proteins. We conclude that PELP1 is a critical mediator of E2 neuroprotection and that PELP1 could potentially play a key role in E2's prevention of JNK activation and AD-related protein induction following ischemic stress. Collectively, these studies shed light on the complex mechanisms underlying the enhanced risk of dementia following surgical menopause and underscore the importance of ovarian conservation and/or E2 therapy following premature menopause in women.