Sex steroids are important regulators of neuronal cell morphology, and this is thought to be critical for gender-specific differences in brain function and dysfunction. Neuronal morphology is controlled by multiprotein complexes including moesin (a member of the ezrin/radixin/moesin (ERM) family), focal adhesion kinase (FAK) or the WASP-family verprolin homologous (WAVE1) protein, all contributing to dynamic remodeling of the cytoskeleton and cell membrane. We investigated the actions of natural progesterone (P) and of the synthetic progestin medroxyprogesterone acetate (MPA) on actin cytoskeleton remodeling, focal adhesion complex formation and actin branching in rat cortical neurons. Treatment with P and, to a lesser extent, MPA, increases the number and density of dendritic spines. P increases the phosphorylation of moesin, FAK and WAVE1, and their redistribution toward cell membrane sites where spines are formed. Signaling to moesin is achieved by PR via a G?i/Gß-dependent signaling to the small GTPase RhoA and its related kinase, Rho-associated kinase-2 (ROCK-2). In parallel, WAVE1 recruitment is triggered by a G?i/Gß-dependent signaling of PR to c-Src, FAK and Rac1 GTPase. Rac1 recruits cyclin-dependent kinase-5 (Cdk5), which phosphorylates WAVE1. Silencing of moesin, FAK or WAVE1 abrogates the increase in dendritic spines induced by progesterone. In all applications, MPA is found to act similar to P, albeit with a lower efficacy. In conclusion, our findings indicate that the control of actin polymerization and branching and focal adhesion complex formation via moesin, FAK and WAVE1 is a key function of progesterone receptor in neurons, which may be relevant for the regulation of dendritic spine turnover and neuronal plasticity.