The transmembrane receptor Notch, a master developmental regulator, controls gliogenesis, neurogenesis, and neurite development in the nervous system. Estradiol, acting as a hormonal signal or as a neurosteroid, also regulates these developmental processes. Here we review recent evidence indicating that estradiol and Notch signaling interact in developing hippocampal neurons by a mechanism involving the putative membrane receptor G protein-coupled receptor 30. This interaction is relevant for the control of neuronal differentiation, since the downregulation of Notch signaling by estradiol results in the upregulation of neurogenin 3, which in turn promotes dendritogenesis.

Keywords: dendritogenesis, estrogen receptors, G protein-coupled estrogen receptor, G protein-coupled receptor 30, hairy and enhancer of split, neurogenin 3
FIGURE 1 | Notch signaling represses dendritogenesis in developing hippocampal neurons by downregulating the expression of neurogenin 3. The binding of Notch ligands (Delta-like, Jagged) results in the cleavage of Notch and the release of an active intracellular domain that is translocated to the cell nucleus where it enhances the transcription of target genes, such as Hes1, that repress the transcription of Ngn3. Ngn3 encodes for a protein, neurogenin 3, which promotes dendritogenesis.

CROSS-TALK BETWEEN ESTRADIOL AND NOTCH SIGNALING
Cross-talk between estradiol and Notch signaling has been detected in breast cancer cells and endothelial cells (Soares et al., 2004; Sobrino et al., 2009). Furthermore, the estrogenic compound genistein downregulates Notch-1 in prostate cancer cells (Wang et al., 2006, 2011). In breast cancer cells, estradiol decreases Notch transcriptional activity via an estrogen receptor (ER) γ-mediated inhibition of Notch cleavage by γ-secretase (Rizzo et al., 2008). In turn, Notch-1 activates ERα-dependent transcription in these cells in the presence or absence of estradiol (Hao et al., 2010). Therefore, estradiol regulates Notch signaling and Notch signaling regulates estrogen signaling in breast cancer cells. It remains to be determined whether the cross-regulation of estrogen and Notch signaling also occurs in other cell types. Given the importance of Notch signaling for brain development, it is important to explore whether such interaction takes place in neural cells.

Recent studies have shown that estradiol reduces the levels of the intracellular transcriptionally active domain of Notch-1 in hippocampal slice cultures (Bender et al., 2010). This suggests that estradiol may decrease Notch-1 mediated transcription in hippocampal cells by reducing Notch-1 cleavage (Figure 1). In primary cultures of mice hippocampal neurons, estradiol decreases the expression of Hes1 and increases the expression of Ngn3 (Ruiz-Palmero et al., 2011). These findings further indicate that estradiol downregulates Notch signaling in hippocampal neurons (Figure 2).

G protein-coupled receptor 30 (GPR30), also known as G protein-coupled estrogen receptor (GPER), is a putative membrane associated ER (Prossnitz et al., 2008; Olde and Leeb-Lundberg, 2009; Prossnitz and Maggiolini, 2009; Langer et al., 2010). GPR30 seems to be involved in the regulation of Notch signaling in hippocampal neurons, since G1, a ligand of GPR30 that imitates the effects of estradiol in different cell types and tissues (Terasawa et al., 2009; Zhang et al., 2010) also imitates the effect of estradiol on Ngn3 expression in hippocampal neurons (Ruiz-Palmero et al., 2011). In contrast, neither the ERα agonist 4,4′,4″-(4-Propyl-[1H]-pyrazole-1,3,5-triyl) trimphenol (PPT) nor the ERβ agonist 2,3-bis-(4-Hydroxyphenyl)propionitrile (DPN) affect the expression of Ngn3 in hippocampal neurons (Ruiz-Palmero et al., 2011). In addition,
1,3-Bis (4-hydroxyphenyl)-4-methyl-5-[4-(2-piperidinylethoxy)phenol]-1H-pyrazole (MPP) and 4-[2-Phenyl-5,7-bis (trifluoromethyl) pyrazolo [1,5-α] pyrimidin-3-yl] phenol (PHTPP), selective antagonists of ERα and ERβ mediated transcription, respectively, do not antagonize the effect of estradiol on Ngn3 expression (Ruiz-Palmero et al., 2011). Furthermore, ICI 182,780 (ICI), antagonist of both ERα and ERβ mediated transcription and agonist of GPR30 (Thomas et al., 2005), not only does not block, but even imitates, the effect of estradiol on Ngn3 expression (Ruiz-Palmero et al., 2011). Therefore, estradiol may regulate Ngn3 levels in hippocampal neurons by a non-canonical mechanism, which probably is independent of classical nuclear ER mediated transcription.

**ESTRADIOL PROMOTES DENDRITOGENESIS IN HIPPOCAMPAL NEURONS BY A MECHANISM INVOLVING Ngn3**

The neuritogenic action of estradiol is mediated by the activation of the mitogen activated protein kinase (MAPK) cascade among other signaling mechanisms (Carrer et al., 2003, 2005; Dominguez et al., 2004; Gorosito and Cambiasso, 2008; Miñano et al., 2008). Recent studies have assessed whether Notch signaling is also involved in the neuritogenic actions of estradiol. Estradiol promotes dendritogenesis in primary hippocampal neurons in culture; this effect is imitated by G1 and it is not blocked when Ngn3 is downregulated using Ngn3-specific siRNA oligonucleotides (Ruiz-Palmero et al., 2011). Therefore estradiol and G1 may act through common mechanisms to regulate Ngn3 expression and dendritogenesis by the inhibition of Notch signaling (Figure 2).

**CONCLUSION**

The studies reviewed here indicate that estradiol interacts with Notch signaling in the nervous system. Estradiol regulates dendritogenesis in developing hippocampal neurons through the modulation of Notch signaling and the upregulation of Ngn3 by a mechanism involving the putative membrane ER GPR30. Further studies are necessary to determine whether this mechanism also operates in other neuronal types. In addition, new experiments are needed to clarify the molecular mechanisms linking estrogen/GPR30 and Notch signaling in neurons.

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