Locally produced neurosteroids are proposed to have many functions in the central nervous system. The identification of the steroidogenic acute regulatory protein in steroid-producing neural cells provides a new tool to understand the sites, regulation, and importance of their synthesis.

Keywords: STAR, neurosteroid, P450scc, steroidogenic acute regulatory protein, STARD1, cholesterol, brain

INTRODUCTION
While the ovary, testes, and adrenal gland generate neuroactive steroids that impact brain function, the central nervous system (CNS) itself generates smaller levels of steroids (neurosteroids) de novo from cholesterol (Corpechot et al., 1983). The enzymes responsible for steroid synthesis localize to specific cell types within the CNS, including the two mitochondrial proteins that initiate steroidogenesis, cytochrome P450 side-chain cleavage (P450scc), and the steroidogenic acute regulatory protein (StAR/STARD1; Compagnone and Mellon, 2000; King et al., 2002).

Steroid hormone production begins with the conversion of cholesterol to pregnenolone by P450scc on the matrix side of the inner mitochondrial membrane (Bhangoo et al., 2006). Depending on the cell type, pregnenolone is further metabolized to other steroids, such as progesterone, allopregnanolone, and estrogen. The rate at which P450scc generates the steroid is determined by its access to cholesterol substrate. This access is controlled by StAR, which catalyzes the delivery of cholesterol from the outer mitochondrial membrane to the inner and P450scc (Figure 1; Clark et al., 1994).

Surprisingly, StAR elicits this intermembrane transfer from outside the mitochondria, prior to its import into the organelle, and processing to its mature 30-kDa forms (reviewed in Bhangoo et al., 2006). This makes its difficult-to-detect 37-kDa “precursor” the active form of StAR, solely due to its positioning outside the mitochondria. Import ends StAR activity. Thus, ongoing steroid synthesis requires ongoing synthesis of StAR.

In summary, the capability and capacity of a cell to make steroid is identified by the presence of P450scc. The rate and level of steroid production is marked by the expression level of StAR. Loss of either protein causes a catastrophic loss of circulating steroids (Hasegawa et al., 2000; Hu et al., 2002). While most research on StAR relates to its role in classic endocrine tissues in the gonads and adrenal gland, recent attention has turned to its importance in neurosteroid production in the CNS.

EXPRESSION OF StAR IN THE ADULT AND DEVELOPING CNS
The presence of StAR mRNA and protein in the CNS was first unambiguously demonstrated by Furukawa et al. (1998) and King et al. (2002) respectively. Subsequent research demonstrated the conservation of its presence in the brain evolutionarily, such as in the songbird and the eel (Li et al., 2003; London et al., 2006; London and Schlinger, 2007). Other data provide conflicting data for the expression and extent of expression of StAR in the fish brain and evidence for very low expression in the CNS of the stingray (Bauer et al., 2000; Kusakabe et al., 2002; von Hofsten et al., 2002; Nunez et al., 2005; Nunez and Evans, 2007).

Like P450scc and the enzyme that converts pregnenolone to progesterone, 3β-hydroxysteroid dehydrogenase (3β-HSD), the level of StAR in the brain is much lower than in endocrine tissues – approximately 0.1–1% of that found in the adrenal (Guennoun et al., 1995; Furukawa et al., 1998). However, StAR itself is expressed at a level much lower than 3β-HSD, but at least an order of magnitude greater than P450scc in the rat CNS (Mellon and Deschepper, 1993; Guennoun et al., 1995; Sanne and Krueger, 1995; Furukawa et al., 1998). Still, local concentrations of neurosteroids produced by neural cells can be far greater than that in serum.

Consistent with its critical role in steroidogenesis, StAR co-localizes with P450scc in the CNS (King et al., 2002). Steroidogenic regions marked by StAR and P450scc include...
the cortex, hippocampus, hypothalamus, cerebellum, and cranial nerve motoneurons (Compagno et al., 1995; King et al., 2002; Sierra et al., 2003); summarized in (Do Rego et al., 2009). As with P450scc, StAR is expressed in specific neuronal and astrocyte populations. The two proteins co-localize to individual neuronal and glial cell types within the neonatal and adult brain (Mellan and Deschepper, 1993; Furukawa et al., 1998; King et al., 2002, 2004a). Specific cell types in the retina and Schwann cells synthesize both StAR and P450scc and hence, neurosteroids (Jung-Testas et al., 1989; Guarneri et al., 1994; Compagno et al., 1995; Koenig et al., 1995; Patte-Mensah et al., 2003; Provost et al., 2003; Benmessahel et al., 2004).

The ability of the brain to synthesize neurosteroids is acquired early in development (Compagno et al., 1995; Pezzi et al., 2003; King et al., 2004a). Embryogenesis marks the time of greatest neuronal growth and development as well as the peak of neurosteroid production. The developing CNS also expresses StAR in dividing cells and germinal layers (Sierra et al., 2003). Neonatal peaks in StAR, P450scc, and aromatase mRNA in Purkinje cells and other cerebellar neurons reflect high levels of de novo synthesis of progesterone and estradiol, which can regulate dendritic growth, spine, generation, and synaptogenesis (Sakamoto et al., 2003). StAR and P450scc in the rat brain, rat C6 glioma cells, and murine astrocytes (Sasso et al., 2010; Raso et al., 2011).

The intracellular mechanism that governs StAR expression in neural tissue has been shown to involve the cAMP second messenger pathway as previously observed in endocrine tissues. Stimulation of the cAMP pathway induces StAR expression and steroidogenesis in neural cells (Papadopoulos and Guarneri, 1994; Rossetti et al., 1994; Arakane et al., 1997; Mellon et al., 2001; King et al., 2002; Jo et al., 2005; Lavaque et al., 2006; Manna et al., 2006; Karri et al., 2007). In one notable but unexplained exception, StAR mRNA levels decline with cAMP stimulation in Schwann cells in spite of increased neurosteroid production (Benmessahel et al., 2004). A preliminary report with an inflammatory model in mice indicates that StAR levels in the spinal cord as in testicular Leydig cells are derepressed with downregulation of COX-2, increasing analgesic neurosteroid production (Wang et al., 2003; Incioglu et al., 2008). This effect on StAR may require increased cAMP.

**TRANSCRIPTION FACTORS CONTROLLING STAR EXPRESSION**

The trans-acting factors controlling StAR gene expression in the CNS remain elusive. The effect of PEA is mediated through its binding of the peroxisome-proliferator activated receptor (PPAR)-α (Sasso et al., 2010; Raso et al., 2011). As in ovarian theca cells and mouse K28 Leydig cells, chronic stimulation with retinoic acid increases StAR and steroid production in GI-1 human glia cells (Kushida and Tamura, 2009; Lavoie and King, 2009). In contrast, long-term treatment with retinoid X and retinoic acid receptor ligand 9-cis-retinoic acid has no effect on StAR gene expression in rat hippocampal slices (Munetsuna et al., 2009b).

Interestingly, steroidogenic factor 1 (SF-1/NR5A1) and DAX-1 which are critical in StAR gene regulation in endocrine tissues, appear to be mostly or entirely uninvolved. This is evidenced by the very limited number of regions expressing these transcription factors compared to StAR. Both SF-1 and DAX-1 localize to the rodent ventral medial hypothalamus (VMH; Guo et al., 1995; Ikeda et al., 1995, 1996; Shinoda et al., 1995b). In one report, SF-1 was identified in hippocampal neurons, with expression overlapping StAR and aromatase (Wehrenberg et al., 2001). Targeted knockout of the transcription factor disrupts the organization of the ventromedial nucleus (Shinoda et al., 1995a; Ikeda et al., 1996) and causes increased anxiety-like behavior (Kim et al., 2009). However, these changes are apparently unrelated to changes in neurosteroid production (Bhangoo et al., 2006; Kim et al., 2008).

An exciting aspect of neurosteroids is that certain neurosteroids such as allopregnanolone exert non-genomic changes primarily through ion channels found in target cells on the order of seconds to minutes. By implication, neurosteroids should be synthesized within a similar time frame. However, such rapid changes in de novo synthesis, while they may exist, have yet to be demonstrated. Such a change would likely involve translational or
post-translational regulation of StAR, such as an activating phosphorylation of the protein by PKA (Rossetti et al., 1994; Arakane et al., 1997; Mellon et al., 2001; King et al., 2002; Jo et al., 2005; Lavaque et al., 2006; Manna et al., 2006). Increases within 5 min in steroid production have been observed in peripheral tissues, such as adrenocortical cells (DiBartolomeis and Jefcoate, 1984). It should be noted that other studies, primarily in birds, describe rapid (on the order of 5–10 min) changes in the levels of aromatase and 3β-HSD activities that result in modest alterations in the levels of neurosteroids metabolized from steroids obtained from peripheral sources (Balhazart et al., 2006; London et al., 2009).

ROLE OF STAR IN THE BRAIN
The multiplicity of regions expressing StAR and P450scC reflects the roles for a neurosteroids in a variety of CNS functions. By example, social isolation stress increases StAR expression in the hippocampus to elevate estrogen levels (Munetsuna et al., 2009a). Conflicting reports exist as to whether ethanol also increases StAR mRNA in the cortex and hippocampus (Serra et al., 2006; Boyd et al., 2010). The hypnotic effect of pentobarbital and antinociceptive activity at the level of the spinal cord are linked to PEA-stimulated StAR-dependent allopregnanolone production in mice (Sasso et al., 2010, 2011). Increased production of StAR and neurosteroids in the spinal cord elicited by select anti-inflammatory factors are linked to antihyperalgesia (Inceoglu et al., 2008). Here, we summarize other studies that specifically describe the involvement of StAR.

SEXUAL FUNCTION
Neurosteroids and the proteins responsible for their synthesis like StAR and P450scC are found in structures relevant for sexual behavior and reproduction, such as the amygdala, medial preoptic area, and VMH (Compagnone et al., 1995; King et al., 2002; Sierra et al., 2003; King, 2008). The importance of neurosteroid production in reproduction is exemplified by the finding that inhibition of hypothalamic progesterone synthesis blocks the ovulatory LH surge in female rats (Micevych et al., 2003). The protein is also found in pituitary gonadotrope LfT2 cells (Lopez de et al., 2007). StAR may serve a different function than in steroid production in these cells since they lack P450scC.

Differences in neurosteroids with gender are mirrored by differences in StAR. Male rats exhibit higher cerebellar levels of StAR, P450scC, and aromatase mRNAs and by implication, higher levels of neurosteroids (Lavaque et al., 2006). The opposite holds true for StAR in the zebra finch (Mirzatoni et al., 2010).

NEUROPROTECTION
Neurosteroids can be neuroprotective and their synthesis changes with aging and injury. Similarly, StAR changes with neuronal insults. For instance, excitotoxic stimuli like kainic acid and NMDA stimulate the generation of StAR and neurosteroids in the hippocampus (Kimoto et al., 2001; Sierra et al., 2003). Damage to the inferior olive elicited by i.p. injection of 3-acetylpiperidine elevates StAR, P450scC, and aromatase mRNA levels in cerebellar neurons (Lavaque et al., 2006). The neuroprotective effects of PEA in murine astrocytes are linked to StAR-dependent allopregnanolone production (Raso et al., 2011).

Changes in neuroprotection and spinal density in hippocampal neurons correlate with StAR-dependent production of estrogen. Knockdown of StAR expression in these neurons reduces estradiol synthesis, increases cell death, reduces proliferation and causes alterations in spine densities, synaptic protein levels, and axon outgrowth in vitro (Fester et al., 2006; Prange-Kiel and Rune, 2006; Prange-Kiel et al., 2006; von Schassen et al., 2006). Given that GnRH can induce hippocampal estradiol synthesis, changes in spine density observed with the ovarian cycle may depend on changes in release of this hormone with the cycle within the hippocampus (Prange-Kiel et al., 2008, 2009).

Aging also increases StAR levels in the rat brain (Sierra et al., 2003). These changes may compose a neuroprotective response, mediated by neurons and astrocytes. Neurodegenerative diseases further evoke StAR expression. Levels of StAR rise in Alzheimer disease, notably in hippocampal pyramidal neurons that express LH receptors (Webber et al., 2006). This rise correlates with a similar increase in LH. In Niemann-Pick disease type C model mice, compromised expression of StAR and consequently, neuroprotective estradiol by affected cortical astrocytes relates to progression of the disease (Chen et al., 2007).

STAR-INDEPENDENT STEROIDOGENESIS
It is important to mention that StAR-independent pathways of intramitochondrial cholesterol transfer do exist, as exemplified in the human placenta, the only steroidogenic tissue known to not express StAR (Bhango et al., 2006). These pathways also reside in StAR-positive cell types, but generate fractional amounts of steroid compared to StAR. These pathways are largely uncharacterized, but contribute to basal steroid production and appear to be unregulated.

Unlike hydrophobic cholesterol, hydroxylated forms of cholesterol (oxysterols) can freely diffuse between mitochondrial membranes to P450scC without the assistance of StAR. Oxysterol-dependent steroid production may be important in testicular development (Hutson, 2006). In the brain, the predominant oxysterol, 24S-hydroxycholesterol, could conceivably represent a source of neurosteroids (Lutjohann et al., 1996; King et al., 2004b).

A role for the peripheral-type mitochondrial benzodiazepine receptor/translocator protein (PBR/TSPO) alone or in coordination with StAR has also been proposed (Papadopoulos, 2004). Endozepines that bind PBR regulate de novo neurosteroid production in C6-2B glioma cells (Papadopoulos et al., 1992). Still, this ubiquitous protein usually exists in the outer mitochondrial membrane as part of the permeability transition pore complex, which controls mitochondrial integrity (Decaudin, 2004). In fact, PBR ligands can induce mitochondrial swelling and are pro-apoptotic (Chelli et al., 2001; Decaudin, 2004). Its knockout is embryonically lethal, reflecting an essential function beyond stereoidogenesis, such as in apoptosis which also affects steroid production (Papadopoulos et al., 1997; King et al., 1998). Correspondingly, knockdown of PBR impairs mitochondrial protein import perhaps secondarily to loss of the electrochemical potential, also crucial to steroid synthesis (King and Stocco, 1996; King et al., 1999, 2000; Hauet et al., 2005). Therefore, while PBR may support carom steroid production, evidence for a direct role is lacking.
CONCLUSION
Current research supports the presence of StAR as a measure of the level of neurosteroid production in the CNS and thus, a tool to probe the importance and regulation of neurosteroids. Factors that control StAR expression and activation control neurosteroid synthesis. The speed with which StAR and thus, neurosteroid synthesis occurs represents a consideration in models of neurosteroid action. Knockouts of StAR and P450scc should disrupt neurosteroid production in the brain and ergo, neurosteroid-regulated functions. Patients with mutations in these proteins present deficits in gonadal and adrenal steroids that manifest as congenital lipoid adrenal hyperplasia and non-classical familial glucocorticoid deficiency type 3 (Lin et al., 1995; Metherell et al., 2009; reviewed in King et al., 2011). The presentation of these conditions in patients and mouse models can include reproductive defects, hypoglycemia, and salt wasting. However, an increased incidence of cognitive deficits and brain developmental or behavioral abnormalities separable from the physiologic phenotype has yet to be established (Bhangoo et al., 2006; Abdulhadi-Atwan et al., 2007). One possibility is that the brain adjusts to the permanent loss of neurosteroids during development. As well, changes in sexual behavior and function could be masked by the overriding effect of the loss of gonadal sex steroid production.

Still, these findings question the significance of neurosteroids. More rigorous and sophisticated studies of patients and knockout animals are required since many studies using inhibitors of steroidogenesis point to a vital role for these compounds in the CNS.

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