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Utilizing induced pluripotent stem cells (iPSCs) to understand the actions of estrogens in human neurons

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ABSTRACT

This article is part of a Special Issue "Estradiol and Cognition".

Over recent years tremendous progress has been made towards understanding the molecular and cellular mechanism by which estrogens exert enhancing effects on cognition, and how they act as a neuroprotective or neurotrophic agent in disease. Currently, much of this work has been carried out in animal models with only a limited number of studies using native human tissue or cells. Recent advances in stem cell technology now make it possible to reprogram somatic cells from humans into induced pluripotent stem cells (iPSCs), which can subsequently be differentiated into neurons of specific lineages. Importantly, the reprogramming of cells allows for the generation of iPSCs that retain the genetic "makeup" of the donor. Therefore, it is possible to generate iPSC-derived neurons from patients diagnosed with specific diseases, that harbor the complex genetic background associated with the disorder. Here, we review the iPSC technology and how it's currently being used to model neural development and neurological diseases. Furthermore, we explore whether this cellular system could be used to understand the role of estrogens in human neurons, and present preliminary data in support of this. We further suggest that the use of iPSC technology offers a novel system to not only further understand estrogens' effects in human cells, but also to investigate the mechanism by which estrogens are beneficial in disease. Developing a greater understanding of these mechanisms in native human cells will also aid in the development of safer and more effective estrogen-based therapeutics.

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Introduction

There are multiple lines of evidence that estrogens exert a powerful influence over cognition (Brinton, 2009; Daniel, 2013; Frick, 2012; Galea et al., 2008; Luine, 2008, 2014). Studies using animal models have demonstrated that estrogens, in particular 17β-estradiol, can influence hippocampal and cortical brain regions to modulate cognitive function, including learning and memory (Frick, 2009; Galea et al., 2008; Luine, 2008). This is in addition to the effects 17β-estradiol has on reproductive and sexual behaviours, regulated by its actions in the hypothalamus (Micevych et al., 2009; Roepke et al., 2011). At the cellular levels, the effects on cognitive function are thought to be driven by 17β-estradiol's effects on synapse structure and function (Brinton, 2009; Srivastava et al., 2013). In addition to these neurotrophic effects, multiple studies have also indicated that 17β-estradiol has potent neuroprotective actions (Arevalo et al., 2015), and has been suggested to be a possible therapeutic avenue for the treatment of several neurodevelopmental, psychiatric and neurodegenerative disorders (Gillies and McArthur, 2010; Hughes et al., 2009; Srivastava and Penzes, 2011).

To date, much of our understanding of the molecular and cellular mechanisms that underlie the effect of estrogen have come from animal based in vitro and in vivo models. Conversely, our understanding of the mechanisms that underlie estrogens' effects in human neurons is limited. Indeed, it has not been possible to investigate the actions of estrogens at a molecular level in native human neurons, and thus to validate whether or not the actions of estrogens as determined in animal models are comparable to its actions in human neurons. This is in part due to the availability of, and the ethical considerations when using human tissue. These issues result in the lack of a suitable and reproducible cellular system that faithfully recapitulates a human neuronal cellular environment and that allows detailed cellular and molecular studies to be carried out. It is also important to recognise that while animal studies support a beneficial role for estrogens in a range of neurodevelopmental, psychiatric and neurodegenerative disorders, how these data translates to humans is unclear. This is particularly important, when considering that there has not been much success in translating preclinical work into novel therapeutic agents to treat

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debilitating neurological, neurodevelopmental or neurodegenerative disorders. This lack of conversion is due to many factors, but are likely to include species differences, differences in brain complexity and disease-specific phenotypes (Dragunow, 2008). Another important factor to consider is the potential negative effects of estrogen, or estrogen-based therapies such as increased risk of cardiovascular problems and increased risk of developing cancers. An alternative approach would be to mimic estrogenic-mediated positive effects by modulating specific ERs (Hughes et al., 2009; Zhao et al., 2005) and/or regulating 17β-estradiol intracellular molecular targets. Such strategies could exploit the beneficial effects of estrogens without the harmful side effects. Therefore, in order to utilize estrogens or estrogen-based therapeutic for the treatment of neurodevelopmental or neurodegenerative disorders, a greater understanding of the effects these compounds have on native human cells and in a disease context is critical (Gillies and McArthur, 2010; Hughes et al., 2009; Srivastava and Penzes, 2011).

Recent advances in stem cell biology are now providing us the tools in which to study basic and disease mechanisms in native human neurons (Brennand et al., 2012; Cocks et al., 2014; Dolmetsch and Geschwind, 2011; Gaspard and Vanderhaeghen, 2011). This has led to the ability to reprogram patient somatic cells into human induced pluripotent stem cells (hiPSCs) and the subsequent differentiation into neurons of specific lineages (Dolmetsch and Geschwind, 2011; Gaspard and Vanderhaeghen, 2011). Importantly, these cells encapsulate and recapitulate the genetic landscape and cellular abnormalities associated with complex disease (Durak and Tsai, 2014; Yu et al., 2013). Critically, this approach provides a potentially limitless source of live human cells for understanding basic neurobiology and disease pathophysiology, and for modelling the actions of potential drug targets (Brennand et al., 2012; Cocks et al., 2014; Dolmetsch and Geschwind, 2011; Gaspard and Vanderhaeghen, 2011). In this review, we will review a) the evidence that estrogens influence human cognition and maybe beneficial in the treatment of neurodevelopment/psychiatric disorders; b) recent advances in our ability to generate hiPSCs and their use in elucidating both basic and disease relevant mechanisms; c) the current limitations and efforts to overcome them when using iPSCs; and d) present some preliminary data demonstrating that neurons differentiated from hiPSCs are responsive to 17β-estradiol treatment.

How do estrogens influence cognition?

During early brain development 17β-estradiol has many roles, ranging from the control of cell proliferation and apoptosis to synaptogenesis and neurogenesis (McCarthy, 2008; Sakuma, 2009). In addition, 17β-estradiol is a critical factor in determining sexual differentiation during development. It has an organisational role which contributes to the establishment of sex differences by influencing the sexually dimorphic formation of the neural circuitry that encodes reproductive and socio-aggressive behaviours (H. Lee et al., 2014; Ubuka and Tsutsui, 2014; Unger et al., 2015; Yang and Shah, 2014). Accumulating evidence indicates that 17β-estradiol's ability to regulate synapse structure and function, and thus neural circuitry, underlies its influence over cognitive function (Luine and Frankfurt, 2012; Sellers et al., 2014; Srivastava et al., 2013). In the cortex and hippocampus, 17β-estradiol has been shown to modulate dendritic spine and synapse formation and density (Luine and Frankfurt, 2012; Srivastava et al., 2013), long-term potentiation (LTP) (Foy et al., 1999; Kramar et al., 2009; Xiao et al., 2012) and long-term depression (LTD) (Mukai et al., 2007). Indeed, regulation of these cellular parameters are thought to be key events and cellular correlates of memory and learning (Fu and Zuo, 2011; Holtmaat and Svoboda, 2009; Malenka and Bear, 2004; Morris, 2003).

The actions of 17β-estradiol are mediated by the classic estrogen receptors (ERs) ERα, ERβ, as well as the G-protein coupled receptor, GPER1 (Brinton, 2009; Sellers et al., 2014; Srivastava and Evans, 2013). These receptors mediate both rapid, membrane-initiated signalling and longer-term/chronic actions via the regulation of gene transcription (Brinton, 2009; McCarthy, 2008; Srivastava et al., 2013). Both ERα and ERβ dimerize in response to 17β-estradiol binding, and subsequently translocate to the nucleus, where they can bind and influence the expression of certain genes (Greene et al., 1986). However, there is a growing appreciation that 17β-estradiol can act via ERα, ERβ and GPER1 to rapidly regulate non-classical signalling resulting in a modulation of cellular physiology (Spencer et al., 2008; Srivastava et al., 2013; Woolley, 2007). Activation of these non-classical pathways by 17β-estradiol can result in multiple cellular effects, including immediate effects on cell physiology and even on protein synthesis or gene transcription (Sellers et al., 2014). Importantly, signalling via specific ERs and the activation of these pathways have also been shown to be required for 17β-estradiol-mediated enhancements of cognitive function (Ervin et al., 2013; Frick, 2012; Gabor et al., 2015; Hawley et al., 2014; Luine and Frankfurt, 2012; Srivastava et al., 2013). It is also important to note that the precise establishment of neural circuitry during development, as well as the proper regulation and maintenance of synaptic connectivity throughout the lifetime of an animal, is essential for normal brain/cognitive function. Indeed disruptions in these process are thought to be a major contributing factor to a number of neurodevelopmental and neurodegenerative disorders (Penzes et al., 2011; Tau and Peterson, 2010; van Spronsen and Hoogenraad, 2010). As such, the ability of 17β-estradiol to regulate synapse structure and function may contribute to its beneficial effects in disease (Srivastava and Penzes, 2011; Srivastava et al., 2013).

While the effects of estrogens on cognition have been well established in animal models, the reported effects of estrogens on cognitive function in human have been much more varied (Luine, 2014; Sherwin, 2012). Nevertheless, multiple studies in human females have reported that administration of estrogens have a positive effect on cognitive function, including memory (Duff and Hampson, 2000; Hampson and Morley, 2013; Hogervorst and Bandelow, 2010; Sherwin, 2012; Smith et al., 2006). In addition, several studies have suggested that 17β-estradiol levels correlate with cognitive performance. For example, during the midluteal phase when 17β-estradiol levels are at their relative height, women have been shown to have a transient increase in performance in typically female-favouring measures of cognition such as verbal fluency. This is opposed to the menstrual phase in these same women, during which 17β-estradiol decline correlates with a transient increase in performance in typically male-favouring measures of cognition such as spatial ability (Hampson, 1990). This relationship between estrogen concentration and cognition has since been reiterated by several studies (Hampson and Morley, 2013; Hogervorst et al., 2004; Phillips and Sherwin, 1992b). In addition, the loss of estrogens (and other steroids) following menopause has been suggested to dramatically increase a woman's risk of memory loss (Maki and Henderson, 2012; Ryan et al., 2012). Interestingly, it has also been shown that this decline can be attenuated by administering exogenous estrogens relatively early in menopause (Phillips and Sherwin, 1992a; Sherwin, 1988). However not all studies have reported positive effects on cognition, with studies reporting no or even negative effects (Daniel, 2013; Hogervorst and Bandelow, 2010; Luine, 2014; Sherwin, 2012). As discussed by Luine (2014) in the primer for this special issue, the variation seen in human studies could be due to difficulties in experimental design or potential environmental cofounders. However, another possibility is that estrogens do not affect human cognition in the same manner as that seen in animal models, due to differences in the basic underlying molecular and cellular mechanisms.

Estrogens and disease: therapeutic potential?

There is also substantial evidence that estrogens exert neuroprotective effects and may also have beneficial effects in animal models of disease (Arevalo et al., 2015; Frick, 2012; Gillies and McArthur, 2010). Preclinical studies have provided evidence that estrogen, or estrogen-

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