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Research report

Sexual dimorphic expression of TrkB, TrkB-T1, and BDNF in the medial preoptic area of the Syrian hamster

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ABSTRACT

Neurotrophins regulate many aspects of neuronal function and activity. Specifically, the binding of Brain-derived neurotrophic factor (BDNF) to Tyrosine receptor kinase-B (TrkB) or its truncated version, TrkB-T1, can cause growth and differentiation or dominant inhibition of receptor signaling, respectively. There is evidence that these neurotropic effects on nervous tissue, in both the central and peripheral nervous system, behave differently between the sexes. This study used western blots to examine the expression of these neurotrophins in the medial preoptic area (MPOA), a sexually dimorphic region of the hamster brain that controls male sex behavior. We report that TrkB-FL and BDNF show greater expression in male MPOA tissue, when compared to female. On the contrary, TrkB-T1 is expressed in greater abundance in the female MPOA. Our results indicate a clear sexual dimorphism of neurotrophins in the MPOA of the Syrian hamster. Furthermore, the greater expression of TrkB-FL and BDNF in the male MPOA suggests that these neurotrophins could be promoting synaptic growth to facilitate male-typical copulation. In contrast, the greater TrkB-T1 expression in the female MPOA suggests a possible inhibition of synaptic growth, and may contribute to the lack of male-typical copulation. Altogether, our data suggests that neurotrophins may play a larger role sexual differentiation than previously thought.

1. Introduction

The medial preoptic area (MPOA) plays a critical role in the regulation of male copulatory behavior in a multitude of species studied to date (Dominguez and Hull, 2005). In the Syrian hamster the magnocellular region of the medial preoptic nucleus (MPN mag), a subdivision of the MPOA, plays a critical role in the regulation of male copulatory behavior. Ablation of this area eliminates male, but not female, sexual behavior (Powers et al., 1987). The MPN mag integrates steroidal and pheromonal inputs to regulate male copulation (Wood and Newman, 1995). For example, testosterone upregulates dendritic spines in the male MPN mag (Garelick and Swann, 2014). Furthermore, the MPN mag's response to pheromones is sexually dimorphic as exposure to female hamster vaginal secretions stimulates the expression of c-fos protein in the male, but not female MPN mag (Fiber and Swann, 1996). Despite this clear sexual dimorphism, the underlying mechanisms remain elusive.

Neurotrophins are a small class of proteins, specific to neural tissue (Lewin and Barde, 1996), that regulate many functions of neural activity. Specifically, brain-derived neurotrophic factor (BDNF), a secreted neurotrophin, regulates neuronal survival, differentiation, and synaptic plasticity (Atwal et al., 2000; Johnson et al., 1986; Park and Poo, 2013; Segal and Greenberg, 1996; Thomas et al., 1992). BDNF acts on neural tissue by binding to its high-affinity receptors, Tyrosine receptor kinase-B (TrkB). The TrkB receptors have at least three isoforms, one full-length (TrkB-FL) and two truncated isoforms lacking the catalytic kinase domain, TrkB-T1 and TrkB-T2 (Klein et al., 1990). The functions of these receptors vary drastically as BDNF binding with TrkB-FL promotes synaptic growth and plasticity, but binding to the truncated receptor has dominant, inhibitory effects on BDNF induced neurotrophin signaling (Eide et al., 1996; Fenner, 2012).

There is growing evidence in support of neurotrophin regulation of sexual dimorphism in both the peripheral and central nervous systems. In the peripheral nervous system, Liu et al. (2012) found that TrkB-T1 expression is androgen-dependent and leads to the selective downregulation of sensory neurons in the mammary gland, assuming a male-typical phenotype. In the central nervous system, the mouse hippocampal CA1 region of proestrous females exhibited greater phosphorylated TrkB-FL (activated) than males (Spencer-Segal et al., 2011). The dimorphic expression of neurotrophins have implications for behavior as parvalbumin-positive cells with a TrkB-FL knockout increased anxiety-like

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behaviors in female mice (Lucas et al., 2014). To date, very few studies have examined sex differences in the expression of growth factors in other areas of the limbic system (Chan and Ye, 2017). The current study explores sex differences in neurotrophins as a possible mechanism of action by examining protein expression of TrkB-FL, TrkB-T1, and BDNF in the MPOA of the Syrian hamster. As the preoptic area plays a critical role in sex-specific behaviors, examining the distribution of these neurotrophins is an important first step in determining their role.

2. Results

Our data indicate that the expression of both BDNF (*P < 0.005, d = 4.74, n = 4) and TrkB-FL (*P < 0.005, d = 6.47, n = 4) proteins are greater in male MPOA (Fig. 1A &1B). In contrast, the expression of the TrkB-T1 receptor is greater in female MPOA tissues (Fig. 1C, *P < 0.005, d = 19.82, n = 4).

3. Discussion

Our data indicates a clear sex difference in the MPOA for the proteins TrkB-FL, TrkB-T1, and BDNF. The data shows an inverse, sex-specific relationship between the two TrkB receptors. The high expression of BDNF and TrkB-FL in the MPOA of the male suggest a role for growth factors in the regulation of male sexual behavior. Conversely, the low expression of BDNF and TrkB-FL in the female are consistent with the decrease in synaptic transmission we have reported in the female MPOA (Fiber and Swann, 1996). The higher levels of TrkB-T1 in the female MPOA may contribute to the decrease in synaptic transmission by inhibiting TrkB-FL/BDNF signaling (Eide et al., 1996). Taken together, our results suggest a role for TrkB-T1 in mediating sex differences in neural transmission and synaptic morphology suggested by our earlier work (Fiber and Swann, 1996; Garelick and Swann, 2014).

Similar to our results, previous studies have found sex differences in TrkB receptors, and their ligand BDNF, in a number of brain areas that may be sex or species dependent (Bakos et al., 2009; Bland et al., 2005; Chen et al., 2005; Dittrich et al., 1999; Franklin and Perrot-Sinal, 2006; Rasika et al., 1999; Snigha et al., 2011; Szapacs et al., 2004; Xu et al., 2015). While none of these studies have examined neurotrophin sex differences in the MPOA, a sexual dimorphism in BDNF expression has been reported in the ventral medial hypothalamus (VMH) (Liu et al., 2014). As the VMH is strongly implicated in the regulation of female sex behavior (Lee and Pfaff, 2008) these findings are consistent with our hypothesis that BDNF expression may mediate sex specific behaviors.

Sex differences in BDNF and its receptors may be mediated by gonadal steroids. Receptors for gonadal steroids are highest in regions implicated in sex behavior in the Syrian hamster (Wood et al., 1992) and play critical roles in the expression of copulation (Wood and Coolen, 1997). Gonadal steroids have been shown to differently effect neurotrophins. It is known that estradiol directly modulates BDNF expression via estrogen response element (Moreno-Piovano et al., 2014; Sohrabji et al., 1995). Furthermore, estradiol regulates both TrkB and BDNF expression in a variety of neural regions in song birds (Dittrich et al., 1999; Gibbs, 1999; Sohrabji and Lewis, 2006; Solum and Handa, 2002; Tang and Wade, 2012) and mammals (Furuta et al., 2013; Singh et al., 1996; Solum and Handa, 2002). Progesterone (Aguirre and Baudry, 2009; González et al., 2004; Gonzalez Deniselle et al., 2007; Kaur et al., 2007; Singh et al., 1996) and testosterone (Ottem et al., 2007; Purves-Tyson et al., 2015) have also been shown to increase BDNF mRNA and protein in many structures of the central and peripheral nervous system. Additionally, neurotrophin expression varies across the estrous cycle (Scharfman et al., 2003; Cavus and Duman, 2003; Gibbs, 1998) and this study did not explore the effects of the estrous cycle on neurotrophin expression. While it is possible that the results are based on the low expression of BDNF that occurs during diestrus, it is unlikely that this result confounds our data given the small margin of error.

Our data indicates an inverse, sex-specific relationship between the two TrkB receptors. The high levels of BDNF and TrkB-FL in the MPOA of the male suggests a role for growth factors in the regulation of male sex behavior. Conversely, the lower levels of BDNF and TrkB-FL in the female MPOA are consistent with the decrease in synaptic transmission reported previously (Fiber and Swann, 1996). The higher levels of TrkB-T1 in the female may contribute to this role by inhibiting BDNF signaling (Fenner, 2012). TrkB-T1 is known to have a dominant inhibitory effect on the BDNF/TrkB interaction (Eide et al., 1996) and can result in sex-specific neural circuits. Liu et al. (2012) report that axons innervating the male mammary gland have more TrkB-T1 than those in the female, inhibiting the TrkB/BDNF interaction, and leading to a loss in

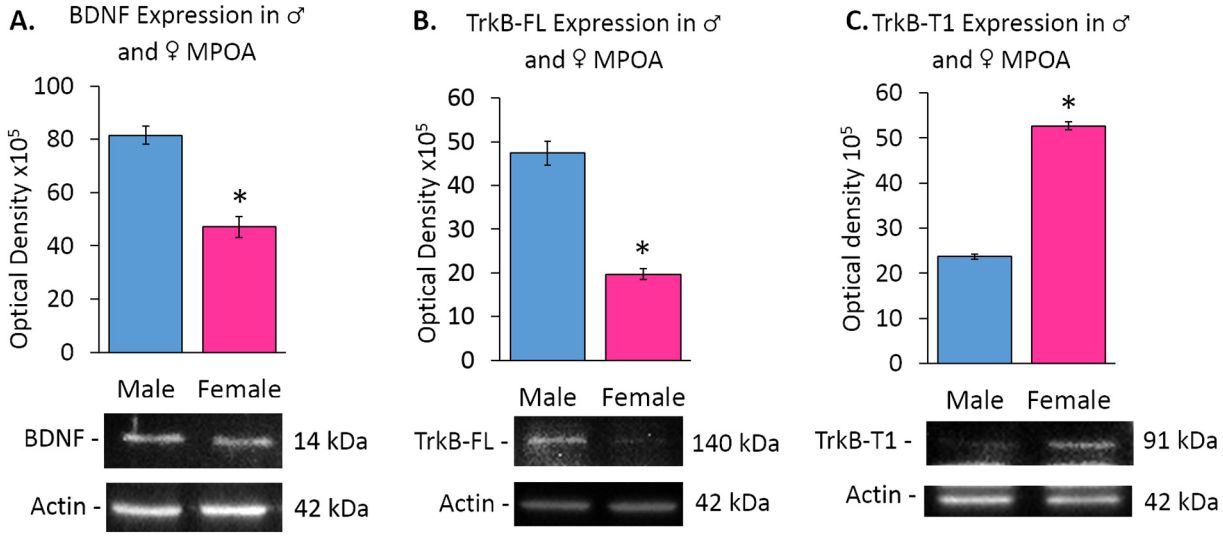

Fig. 1. BDNF (A), TrkB-FL (B), and TrkB-T1 (C) Expression in the MPOA of the male and female Syrian hamster. Optical density described as the density of each band normalized to that of the actin band. Images of representative blots are provided beneath. *Indicates p < 0.05.