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Early life social stress induced changes in depression and anxiety associated neural pathways which are correlated with impaired maternal care

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ABSTRACT

Exposures to various types of early life stress can be robust predictors of the development of psychiatric disorders, including depression and anxiety. The objective of the current study was to investigate the roles of the translationally relevant targets of central vasopressin, oxytocin, ghrelin, orexin, glucocorticoid, and the brain-derived neurotrophic factor (BDNF) pathway in an early chronic social stress (ECSS) based rodent model of postpartum depression and anxiety. The present study reports novel changes in gene expression and extracellular signal related kinase (ERK) protein levels in the brains of ECSS exposed rat dams that display previously reported depressed maternal care and increased maternal anxiety. Decreases in oxytocin, orexin, and ERK proteins, increases in ghrelin receptor, glucocorticoid and mineralocorticoid receptor mRNA levels, and bidirectional changes in vasopressin underscore related work on the adverse long-term effects of early life stress on neural activity and plasticity, maternal behavior, responses to stress, and depression and anxiety-related behavior. The differences in gene and protein expression and robust correlations between expression and maternal care and anxiety support increased focus on these targets in animal and clinical studies of the adverse effects of early life stress, especially those focusing on depression and anxiety in mothers and the transgenerational effects of these disorders on offspring.

1. Introduction

Exposures to various types of early life stress can be robust predictors of the development of psychiatric disorders, including depression and anxiety (Eiland and McEwen, 2012; Heim and Binder, 2012; Heim and Nemeroff, 2001; Heim et al., 1997; Johnson and Sarason, 1978; McEwen, 1998, 2003). Adverse family social environments are strongly associated with the development of depression (Bouma et al., 2008; Essex et al., 2011; Lizardi et al., 1995) and postnatal exposure to maternal depression has negative effects on offspring mental health (Essex et al., 2011; Goodman et al., 2011). It is postulated that maternal depression exerts its adverse influence through impaired mother–infant bonding (Bureau et al., 2009; Gunnar and Vazquez, 2006; Milan et al., 2009).

In rodent dams, chronic social stress (CSS, daily exposure to a novel male intruder) can be used as an ethologically relevant, transgenerational model of the role of stress in the etiology of depression and anxiety in mothers and their offspring (Babb et al., 2014; Carini et al., 2013; Carini and Nephew, 2013; Murgatroyd and Nephew, 2013; Nephew and Bridges, 2011) (see Fig. 1). Exposure of F0 lactating dams to CSS as a model for postpartum depression and anxiety possesses construct and face validity and depresses maternal care and increases anxiety (Carini et al., 2013; Nephew and Bridges, 2011). For the young F1 offspring of stressed F0 dams, CSS is a robust early chronic social stress (ECSS) which includes exposure to both the depressed maternal care from their F0 mothers and the conflict between the F0 dam and the male intruders. Similar to observations in human mothers exposed to high levels of early life stress (Goodman, 2007), the maternal care displayed by F1 dams towards their F2 offspring is also depressed (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013). Furthermore, the social behavior of both male and female F2 offspring (exposed to depressed maternal care from their F1 mothers) is impaired (Babb et al., 2014). Since maternal depression can often be predicted from an exposure to early life stress, the CSS F1 and F2 generations represent relevant models to study the role of ECSS in postpartum depression and anxiety and the adverse effects of these disorders on offspring. Peripheral and central endocrine studies of the CSS model reveal substantial changes in the behaviorally relevant hormones oxytocin (OXT), vasopressin (AVP), prolactin (PRL), estradiol, and corticosterone (Carini and Nephew, 2013; Murgatroyd and Nephew, 2013). In the brain, OXT, AVP, and PRL gene expression are altered in the hypothalamus of ECSS exposed dams (Murgatroyd and Nephew,

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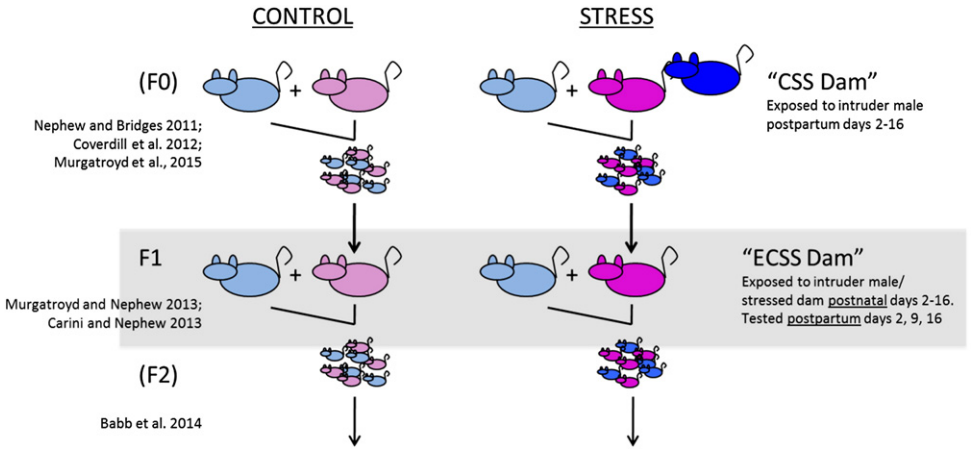

Fig. 1. Diagram of the chronic social stress paradigm. The current study involved the dams from the F1 generation. Testing on postpartum days 2, 9, and 16 included maternal care and maternal aggression. Brain samples from the F1 dams were obtained on postpartum day 23 when the F2 pups were weaned. These samples were analyzed for the expression of oxytocin, oxytocin receptor, vasopression, vasopression V1a receptor, prolactin receptor, glucocorticoid and mineralocorticoid receptors, orexin A, orexin receptors 1 and 2, ghrelin receptor, and protein levels of BDNF, ERK1/2, and phospho-ERK1/2.

2013). OXT, AVP, and PRL are primary mediators of maternal care and have been implicated in the etiology and symptomology of stress related affective disorders (Faron-Górecka et al., 2014; Insel and Young, 2001; Mann and Bridges, 2001; Nephew, 2012; Rilling and Young, 2014; Zamorano et al., 2014). Furthermore, OXT is a key mediator of the reciprocal nature of the mother–infant bond (Carter, 2003; Feldman et al., 2007, 2011; Henriques et al., 2014; MacKinnon et al., 2014; Mogi et al., 2011). The current study investigated additional neural targets that may be involved in the adverse effects of ECSS on the F1 generation and represent novel preventative and/or treatment targets.

The maladaptive impacts of early life stress on mental health are mediated in part through changes the hypothalamic–pituitary–adrenal (HPA) axis (Gunnar and Vazquez, 2006), although there is growing support for the involvement of multiple interacting brain regions and neuroendocrine factors (Lucassen et al., 2014). There is strong evidence that early life stress has persistent effects on the regulation of the HPA axis through altered gene expression in the brain which involves changes in glucocorticoid receptors (GR) (Liu, 1997; Lupien et al., 2009; McGowan et al., 2009; Suderman et al., 2012) as well as more recent data on mineralocorticoid receptors (MR) (Baes et al., 2014; Juruena et al., 2013; Klok et al., 2011a; Young et al., 2003). It has been suggested that MR receptor activity is increased in patients with depression compared to controls, and a systematic review of the role of GR and MR in early life stress related depression concludes that the effects of stress on the GR/MR ratio may be a key etiological factor in depression, although there are few clinical studies that have investigated this role (Von Werne Baes et al., 2012). Given the previously reported HPA changes in the ECSS exposed F1 dams, it was postulated that changes in both MR and GR may mediate these effects.

Recent studies suggest that ghrelin, an orexigenic hormone, may be a primary mediator of the adverse effects of stress on behavior (Ishitobi et al., 2012; Lutter et al., 2008). Although ghrelin is produced in the stomach, it crosses the blood brain barrier (Banks et al., 2002) and ghrelin receptors (GHR) have been found in several brain regions, including the paraventricular nucleus (PVN), amygdala, and ventral tegmental area (VTA) (Alvarez-Crespo et al., 2012; Perello et al., 2012). A Leu72Met polymorphism in the ghrelin gene coding region associates with depression (Nakashima et al., 2008), and elevated ghrelin levels have been found in patients with treatment-resistant depression (Ishitobi et al., 2012), suggesting that ghrelin may be a useful indicator of treatment efficacy. In addition, the orexin system, including the expression of orexin and its receptors (Ox1R and Ox2R) has been implicated in the expression of both maternal care (D'Anna and Gammie, 2006) and depressive behavior and pathophysiology (Arendt et al., 2013; Nollet and Leman, 2013). The clinical and rodent studies indicate that ghrelin and orexin may mediate the depressed maternal care in dams exposed to ECSS.

The brain-derived neurotrophic factor (BDNF) pathway, including extracellular signal regulated kinase (ERK) signaling, is another mechanistic target for depression research. In a rat model of infant maltreatment, decreased BDNF levels were found to be programmed through an epigenetic mechanism (Roth et al., 2009). In mice, the inhibition of ERK signaling in hippocampus induces depression-like behavior and blocks the behavioral effects of antidepressants (Duman et al., 2007; Schmidt and Duman, 2007). Adult rodent exposure to exogenous corticosterone affects phospho-ERK1/2 levels in the dentate gyrus, and these effects are sensitive to antidepressant treatment (Gourley et al., 2008). Long-term changes in the BDNF pathway are associated with childhood adversity and adult depression symptoms (Aguilera et al., 2009; Gatt et al., 2009). Mitogen-activated protein kinase phosphatase-1 (MKP-1) expression is increased in the postmortem hippocampus of patients with major depression compared to healthy controls, and increasing MKP-1 activity in rodent models induces depressive behaviors (Duric et al., 2010) and is further regulated by BDNF (Jeanneteau et al., 2010). In the transgenerational CSS model, we propose that ECSS-induced decreases in the BDNF pathway in a nucleus involved in the processing of rewarding stimuli, the nucleus accumbens, may mediate decreased maternal care and increased anxiety.

The objective of the current study was to augment the previous investigation of the endocrine and behavioral effects of ECSS in the F1 generation of CSS model of depression and anxiety (Carini and Nephew, 2013) with the addition of neuroendocrine analyses of vasopressin, oxytocin, prolactin, ghrelin, orexin, corticosteroid receptors, and ERK pathways. These targets are both translationally and clinically relevant. This broad, yet targeted, approach was taken because complex behaviors including maternal care are dependent upon multiple interacting brain regions, and ECSS may interact with each of these structures in distinct, meaningful ways. ECSS-induced changes in peripheral estrogen, PRL, corticosterone, maternal behavior, and lactation in the F1 dams in this study have been previously reported (Carini and Nephew, 2013). It is hypothesized that AVP, OXT, PRL, orexin and BDNF related gene expression and/or protein levels will be down regulated in key brain regions in ECSS F1 dams, ghrelin receptors, GR and MR will be up-regulated, and these changes will be associated with impaired maternal behavior.