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Research Report

Brain regional differences in social encounter-induced Fos expression in male and female rats after post-weaning social isolation ☆

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ABSTRACT

Early life adversity has been related to a number of psychological disorders including mood and other disorders that can manifest as inappropriate or aggressive responses to social challenges. The present study used post-weaning social isolation (PSI) in rats, a model of early life adversity, to examine its effects on Fos protein expression produced by exposure to a novel social encounter. We have previously reported that the social encounter-induced increase in Fos expression in the medial prefrontal cortex observed in group-housed controls (GRP) was attenuated in rats that had experienced PSI. Here we assessed Fos expression in other brain regions thought to be involved in emotion regulation and social behavior. Male and female rats were housed in same-sex groups or in isolation (ISO) for 4 weeks beginning on postnatal day (P) 21 and were exposed to a single 15 min social encounter with a novel same-sex conspecific on P49. Fos positive cells were assessed using immunohistochemistry in 16 regions within the forebrain. Exposure to a novel conspecific increased Fos expression in the forebrain of GRP rats in a region- and sex-specific fashion. This increase was blunted or absent in ISO rats within many regions including cortical regions, thalamus, habenula, dentate gyrus, lateral septum, and basolateral amygdala. In several regions, the increase in Fos was greater in male than in female group housed rats. Negative relationships were observed between social interactions and Fos in some regions. Forebrain hypofunction produced by early-life adversity may be involved in socially inappropriate behavior.

☆The authors have no conflicts of interest to report.

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1. Introduction

Early life adversity, including during adolescence, is a strong predictor of aggression and antisocial behavior in adults (Haller et al., 2014). Post-weaning social isolation (PSI) of rats or other social species, also known as isolation rearing, is a well-established model of early life adversity that produces inappropriate social behavior and heightened emotional reactivity to social experience. Although long-term social isolation that occurs during different periods of development (either neonatally or in adulthood) may also impact behavior, the alterations in social behavior that are produced by PSI are particularly pronounced (Hall, 1998). These alterations are persistent and in some cases irreversible (Tulogdi et al., 2014), and are thought to be largely due to a lack of opportunities for social play during the sensitive period of adolescence. Play is adaptive in the early life of social species including humans and rodents (Panksepp, 1981), allowing individuals to practice the skills needed for proper social conduct and developmentally appropriate behaviors in adulthood.

PSI consists of depriving adolescent rats of social experience by housing them individually (as compared to housing in same-sex groups, typically 3 or 4 per cage) for a period of 4–8 weeks after weaning at postnatal day 21 (P21). This period encompasses the entire periadolescent period, which in the rat has been described as lasting roughly from P28 to P60 (Spear, 2000). Adolescence in the rat has also been defined as beginning as early as P21 and consisting of early (P21–P30), middle (P30–P45), and late (P45–P60) periods (Tirelli et al., 2003). By isolating rats immediately after weaning it is ensured that the entire periadolescent period is accounted for. Social isolation during this period produces persistent behavioral changes known as the isolation syndrome (Hatch et al., 1965) that includes outcomes such as increased anxiety-like behavior (Einon and Morgan, 1977), overreaction to novelty (Hall, 1998), and altered social behavior (Ferdman et al., 2007; Wongwitdecha and Marsden, 1996). Among the alterations in social behavior produced by postnatal social isolation is increased aggression; PSI of male rats produced increases in aggression (Zhao et al., 2009) and isolation rearing-induced agression was exacerbated when testing occurred in an unfamiliar environment (Wongwitdecha and Marsden, 1996). Although most studies of PSI have been performed in male rats, exposure to PSI can also result in abnormal patterns of social behavior (Hermes et al., 2011), including increased aggression, in females as well as males (Wall et al., 2012).

A number of previous studies have reported that social interaction, including play behavior, produces alterations in the immediate early gene *c-fos* (Gordon et al., 2002; Northcutt and Nguyen, 2014), or in its protein product, Fos (Weathington et al., 2012; Paredes-Ramos et al., 2014), in a number of brain regions, in particular within a network involving corticostriatal and corticolimbic connections (van Kerkhof et al., 2014). Exposure to a novel conspecific can produce differential alterations in mPFC function (Hermes et al., 2011; Levine et al., 2007), including alterations in Fos (Wall et al., 2012) in rats after PSI as compared to normally housed controls. In our previous report, a single, brief social encounter with a novel same-sex rat induced large increases in the expression of Fos in the mPFC of group-reared rats (GRP). The social encounter-induced increase in mPFC Fos expression was profoundly blunted in rats that had experienced PSI. Interestingly, there were subregion differences in the magnitude of the Fos response between GRP males and females; the response was greater in males in the infralimbic region and greater in females in the anterior cingulate (Wall et al., 2012). Because the mPFC is still maturing during the adolescent period, it was of particular interest in studies of adolescent adversity including PSI. However, alterations in other brain regions, including the amygdala (Lukkes et al., 2012) and the hippocampus (Bonab et al., 2012) can also result from PSI.

The goal of the present study was to determine the effects of a brief social encounter on Fos protein expression in multiple cortical and subcortical brain regions to assess whether PSI-induced neuronal hypofunction during social interaction is specific to the mPFC. Fos is a transcription factor that is induced rapidly and transiently in many types of neurons, and is sensitive to neuronal activation in much of the brain (Curran and Morgan, 1995). We were particularly interested in brain regions important for the regulation of emotion and those that may have connections with the mPFC. Thus, we used tissue from the same rats used in Wall et al. (2012) to assess Fos expression in regions within the cortex, thalamus and epithalamus, hippocampus, amygdala, and basal ganglia of male and female rats exposed to either PSI (ISO) or group housing (GRP). An additional goal of the study was to determine relationships between social behavior and Fos activation in the forebrain.

2. Results

PSI blunted the social encounter-induced increase in Fos expression that was observed in GRP rats in most of the brain regions assessed. In several regions the difference was more pronounced in males, in that a social encounter produced greater increases in Fos in GRP males than in GRP females as well as ISO males and females.

2.1. *Cortex and thalamus*

In these regions, a social encounter produced robust increases in Fos expression that only reached significance in GRP males (Fig. 1).

2.1.1. *Piriform cortex*

In the PIR (Fig. 1A) there was a significant Rearing × Social Encounter × Sex interaction, $F(1,55)=7.56$, $p<0.01$. Post-hoc tests indicated that Fos was only induced by a social encounter in GRP males, thus GRP males exposed to a social encounter had significantly more Fos in the PIR than GRP male home cage controls $p<0.05$; no other Social Encounter groups were significantly different than their respective home cage controls. In addition, a significant Rearing × Social Encounter interaction was observed, $F(1,55)=12.64$, $p<0.01$. Post hoc tests collapsed across Sex indicated that Fos expression produced by a social encounter was greater in GRP than