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Research Report

Equal effects of typical environmental and specific social enrichment on posttraumatic cognitive functioning after fimbria-fornix transection in rats ☆

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ABSTRACT

Enriched environment (EE) has been shown to have beneficial effects on cognitive recovery after brain injury. Typical EE comprises three components: (i) enlarged living area providing physical activation, (ii) sensory stimulation, and (iii) social stimulation. The present study assessed the specific contribution of the social stimulation. Animals were randomly divided into groups of (1) a typical EE, (2) pure social enrichment (SE), or (3) standard housing (SH) and subjected to either a sham operation or transection of the fimbria-fornix (FF). The effect of these conditions on acquisition of a delayed alternation task in a T-maze was assessed. The sham control groups were not affected by housing conditions. In the lesioned groups, both typical EE and SE improved the task acquisition, compared to SH. A baseline one-hour activity measurement confirmed an equal level of physical activity in the EE and SE groups. After delayed alternation testing, pharmacological challenges (muscarinergic antagonist scopolamine and dopaminergic antagonist SKF-83566) were used to assess cholinergic and dopaminergic contributions to task solution. Scopolamine led to a marked impairment in all groups. SKF-83566 significantly enhanced the performance of the lesioned group subjected to SE. The results demonstrate that housing in a typical as well as atypical EE can enhance cognitive recovery after mechanical injury to the hippocampus. The scopolamine challenge revealed a cholinergic dependency during task performance in all groups, regardless of lesion and housing conditions. The dopaminergic challenge revealed a difference in the neural substrates mediating recovery in the lesioned groups exposed to different types of housing.

Abbreviations: EE, enriched environment; SE, social environment; SH, standard housing; FF, fimbria-fornix; TBI, traumatic brain injury; DA, dopamine; ANOVA, analysis of variance.

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1. Introduction

In recent years a consensus has emerged, that a typical preclinical enriched environment (EE) holds potential for maximizing treatment effects of restorative therapies after various brain injuries and disorders (Bondi et al., 2014; Hannan, 2014). This kind of typical preclinical EE consists of three basic components: (i) increased opportunity for physical activation and exploration of an enlarged living area, (ii) sensory stimulation from addition of various toys and, (iii) social stimulation from group housing. Housing laboratory animals in an EE has repeatedly been shown to induce a positive effect after traumatic brain injury (TBI) by stimulating neural processes promoting functional recovery (Cheng et al., 2012; de Witt et al., 2011; Hamm et al., 1996; Kline et al., 2012; Matter et al., 2011; Passineau et al., 2001; Sozda et al., 2010; Will et al., 2004). Furthermore, a beneficial effect of EE has also been shown in the intact rodent brain (Bruel-Jungerman et al., 2005; D'Andrea et al., 2007; Doulames et al., 2014; Veena et al., 2009). In response to the advantageous effects of EE on both histological and behavioural outcome after brain injury, the use of preclinical EE is becoming accepted as a valid model of clinical neurorehabilitation (Bondi et al., 2014). Optimization of clinical neurorehabilitation presents a major avenue for improving quality of life of brain injury survivors and reduction of the economic burden on society. A better understanding of the contributions from the three main components of preclinical EE to the therapeutic effects of EE is of substantial importance for the optimization of clinical neurorehabilitation.

Only a few studies have so far investigated the specific effects of social enrichment (SE) in the uninjured brain (Elliott and Grunberg, 2005; Rosenzweig et al., 1978; Schrijver et al., 2004, 2002) and after infliction of brain injury (Johansson and Ohlsson, 1996; Risedal et al., 2002; Sozda et al., 2010). Regarding functional recovery after brain injury, studies mostly report a synergistic effect between the three components (i.e. increased space for physical activation, sensory experience and social stimulation). However, discrepancies exist. Sozda et al. (2010) reported no beneficial effect of pure social housing on cognitive recovery after controlled cortical impact. Johansson and Ohlsson (1996) on the other hand found that animals exposed to social interactions in a solely socially-housed group performed better in locomotor tests than individually housed animals with access to a running wheel after cerebral infarct. But they also found that the EE combining unrestricted physical activity and social interaction resulted in even better performance in a motor task. In contrast, Risedal et al. (2002) found no significant functional difference in motor-planning on the rotarod in rats housed in either EE or SE after cortical infarct. Thus, it appears that the different types of stimulation associated with a typical EE induce different levels of functional recovery, depending on the nature of the outcome measure, e.g. cognitive, motor, social or emotional functioning, and potentially even the type of lesion.

To further investigate the contributions of the social aspect of EE on functional recovery after brain injury, we recently studied the effects of a social intervention resembling that of clinical settings (Gram et al., Unpublished results). The social intervention allowed the rats to have a permanently large social network, combined with the opportunity to interact with initially unknown rats in an environment away from home, either on a daily or weekly basis. The results showed effects of social stimulation in both neurally intact and lesioned animals, but these effects were different across cognitive and emotional domains. Ultimately, the level and type of beneficial effects induced by socialization may be of unequal importance in the intact and injured brain, respectively. For instance, a SE intervention in intact rats may exert limited effects on explorative behaviour (e.g. Zimmermann et al., 2001). In the injured brain on the other hand, it may hold a higher potential for supporting posttraumatic recovery in social and/or emotional domains, rather than in a specific cognitive task. Thus, the potential beneficial effect of a pure social stimulation may be task specific and further influenced by the lesion. In line with that, the present study investigated to what degree a three-week posttraumatic stay in either typical EE or a purely social environment (SE) influences acquisition of a spatial delayed alternation task in a T-maze in both intact and lesioned animals. Furthermore, the neural substrate mediating task solution was examined by administering pharmacological challenges at the end of the task acquisition period. Finally, to evaluate if potential differences in performance were associated with varying degrees of physical exercise, we measured the baseline daily activity in the EE and SE groups during the three-week enrichment period.

The brain injury addressed in the present study was a bilateral transection of the fimbria-fornix (FF) fibre bundle. This lesion causes structural, neurochemical and neurophysiological changes as well as neurodegeneration of the connected structures, hippocampus and septum, and leads to their dysfunction (Cain et al., 2006; Gaskin and White, 2007; Ginsberg and Martin, 2002, 1998; Ginsberg et al., 1999; Mogensen et al., 2007, 2005, 2004a; Oddie et al., 2002). Although the applied model only represents a partial model of brain injury with limited clinical correspondence, fornix and hippocampal atrophies are frequently part of the neuropathological profile of traumatic brain injuries (Bigler et al., 1997; Christidi et al., 2011; Gale et al., 1993; Tate and Bigler, 2000; Yallampalli et al., 2013). With the choice of this animal model and cognitive task, we expand the understanding of the social stimulation aspect of EE, as the data will act as a supplement to previous results investigating spatial learning in a water maze after controlled cortical impact (Sozda et al., 2010) and locomotor activity after cerebral infarct (Johansson and Ohlsson, 1996).

2. Results

2.1. *Anatomy*

The histological examination revealed that in all of the lesioned animals, the fimbria-fornix rostral to the dorsal hippocampus was almost completely transected – only a minor portion of the fibres remained intact. A correlation analysis revealed no significant correlation between percentage of fibres cut by the transection and mean performance in the spatial delayed alternation task ($p=0.126$). The size of lesion in the fimbria-fornix transected groups (FF/SH, FF/EE,