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Research report

Environmental enrichment aides in functional recovery following unilateral controlled cortical impact of the forelimb sensorimotor area however intranasal administration of nerve growth factor does not

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ABSTRACT

Purpose: An injury to the forelimb sensorimotor cortex results in the impairment of motor function in animals. Recent research has suggested that intranasal administration of nerve growth factor (NGF), a protein naturally found in the brain, and placement into enriched environments (EE) improves motor and cognitive function after traumatic brain injury (TBI). The purpose of this study was to determine whether NGF, EE, or the combination of both was beneficial in the recovery of motor function following TBI.
Results: Uninjured animals had fewer foot faults than injured animals, displaying a lesion effect. Injured animals housed in EE were shown to have fewer foot faults whether or not they received NGF. Injured animals also displayed an increased reliance on the non-impaired limb further validating a lesion effect.
Conclusion: EE is an effective treatment on the recovery of motor function after a TBI. Intranasal administration of NGF was found to not be an effective treatment for functional motor recovery after a TBI.

1. Introduction

Traumatic brain injury (TBI) is a common occurrence with very few promising treatments available that could help return patients to their normal level of functioning (Greve and Zink, 2009). The primary injury is the result of tissue damage at the site of trauma within the brain which physically disrupts cell membranes and homeostasis leading to neuronal swelling and other neurotoxic events while the secondary events expands the effect of the injury leading to further physiological insults (Moppett, 2007). Within minutes the consequences of the secondary injury can turn lethal (Moppett, 2007). The secondary insults may include re-perfusion, hypoxia, edema, and ischemia all of which will contribute to the individual's outcome (Lv et al., 2013; Moppett, 2007).

A controlled cortical impact (CCI) device creates a lesion on the animal's brain, simulating what a TBI would be in a human brain. The forelimb sensorimotor cortex (FL-SMC) is located on both the left and right lobes of the brain and assists in motor function (Bury and Jones, 2002). A unilateral CCI to the FL-SMC will result in one side of the animal's body being impaired (contralateral) while the other side is relatively normal (ipsilateral) (Bury and Jones, 2002). Damage unilaterally to the FL-SMC can cause deficits in the somatosensory function and in the use of the contralateral forelimbs (Schallert et al., 2000). With this type of injury, animals depend more on the ipsilateral side because they favor the limb that is still working correctly (Bury and Jones, 2002). Because of the frequent use of the ipsilateral side, neurons of the opposite motor cortex become responsive to changes in forelimb behavior and can promote changes in neural plasticity (Bury and Jones, 2002; Jones et al., 1999, 2012; Schallert et al., 2000). Neural plasticity is influenced by experience, and repetition of tests can cause a positive or negative effect on the results (Jones et al., 1999; Schallert et al., 2000; Will and Kelche, 1992). A forelimb sensorimotor cortex CCI allows researchers to compare the contralateral side to the ipsilateral side and to determine if post-injury behavior modifications will make a significant improvement. Sensorimotor differences can be quantified using the foot fault and limb use tests that in previous studies have been shown to be helpful in recovery of function, as well as assessing for behavioral and pharmacological interventions (Humm et al., 1999; Kawamata et al., 1997; Lv et al., 2013; Schallert et al., 2000).

Enriched environment housing has been shown to improve cognitive and motor function after a TBI (Kline et al., 2010; Peruzzaro

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et al., 2013). An enriched environment (EE) is created when the research animal is housed in an interactive environment with stimulating toys and a social aspect, which by changing and manipulating the environment of the animal has been shown to improve functional outcome after TBI (Kline et al., 2012; Van Praag et al., 2000). An enriched environment is a large single cage that encourages specific social interactions and behaviors (Van Praag et al., 2000). The enriched environment allows the animal to explore, exercise, and interact with other animals creating a stimulating environment for the research animal (Bayona et al., 2005; Hicks et al., 2002). EE housing encourages novel interactions with the environment and other social stimuli which in turn continually stimulates the brain by releasing neural growth factors (Bayona et al., 2005; Hicks et al., 2007). Objects, such as animal friendly toys, can be introduced to promote physical exercise and provide sensory stimulation to the animals (Grealy et al., 1999). In the standard environment (SE), the animal is housed in a standard cage, which does not allow for exercise and social interactions. A previous study found that housing animals in SE caused memory impairment (Kovesdi et al., 2011). Enriched environment also helps to stimulate organization and increase neural structures in the animal's brain (Held et al., 1985; Kovesdi et al., 2011). In previous studies EE has contributed to a better outcome of TBI by positively affecting neurogenesis (Kovesdi et al., 2011). Research has also shown that animals housed in an interactive environment have increased brain weights, thicker cortical areas, and a greater number of functional connections per neuron (Bayona et al., 2005; Kovesdi et al., 2011). The EE increases the amount of sensory stimuli available to the research animal and improves the plasticity of neural networks contributing to synaptogenesis (Bayona et al., 2005; Jones et al., 2012; Van Praag et al., 2000; Will et al., 2004). As a rehabilitation type of treatment, EE is effective and has been shown to lessen post-TBI behavioral deficits (Sozda et al., 2010; Van Praag et al., 2000). Earlier studies have shown that exposure to EE increases the production of nerve growth factor in the cerebellum (Angelucci et al., 2009). Animals exposed to EE have also shown an increase in neurotrophin gene expression which promotes neuronal survival and neural plasticity (Hicks et al., 2002).

Nerve growth factor (NGF) is an essential component necessary to regenerate damaged cells caused by a TBI or other injury and can promote the growth of new cells within brain tissue (Angelucci et al., 2009; Branchi et al., 2006). NGF is a protein naturally found in the brain that aids in neuronal proliferation and differentiation, as well as synaptogenesis, and is thought to help in brain structure and function (Branchi et al., 2006). NGF also plays a role in the development and maintenance of sympathetic and sensory peripheral neurons (Lv et al., 2013). Studies have shown that NGF prevents the loss of phenotype and preserves cholinergic neurons after a TBI by increasing the synthesis of choline acetyltransferase and preventing atrophy of basal forebrain cholinergic neurons (BFCN) following experimental injury (Garofalo and Cuello, 1994). Regular levels of NGF in the brain have been shown in other studies to play a role in neuronal survival and neuronal plasticity (Hicks et al., 2002, 2007). NGF allows neurites to sprout and also helps to restore the function of injured neurons (Bonini et al., 2000). Administering NGF intranasally allows the protein to pass through the blood brain barrier and diffuse within the brain with less difficulty than if given intravenously (De Rosa et al., 2005; Lv et al., 2013). Given intranasally at 50 μl per day for 6–7 days, NGF has been shown to reduce brain edema, improve cognitive function, and motor function after traumatic brain injury TBI (Lv et al., 2013; Tian et al., 2012).

While EE and NGF treatments separately have been shown in previous research to be effective, a combination of the two approaches has yet to be explored. Earlier studies have shown that exposure to EE increases the production of nerve growth factor in the cerebellum (Angelucci et al., 2009). Research animals exposed to EE have shown an increase in neurotrophin gene expression (Hicks et al., 2002). Regular levels of NGF and other neurotropic factors in the brain have been shown in other studies to play a role in neuronal survival and neuronal plasticity (Hicks et al., 2002). Previous research suggests that administering NGF and housing the research animals in an enriched environment may increase the levels of NGF after a brain injury. In one study, when normal animals were housed in EE, an increased level of NGF was found in different parts of the brain (Hicks et al., 2002). However, TBI EE animals with attenuated cognitive deficits did not alter NGF levels (Hicks et al., 2002). A recent study that combined EE and a chronic treatment of 5-HT, a receptor agonist which regulates mood and vascular function found additive effects on the recovery process of TBI (Sozda et al., 2010).

The addition of NGF plus an EE in a TBI expands on previous research; these combined treatments may increase production of nerve growth factor along with stimulating neurons and non-neuronal formation in the injured FL-SMC. In a unilateral CCI of the FL-SMC, an NGF treatment combined with EE will help the contralateral side to regain some function as well as stimulate neural plasticity. The current study was performed in order to evaluate if NGF, EE, or the combination of both will be more beneficial in attenuating deficits caused by TBI.

2. Materials and methods

2.1. Subjects and standard housing

For this study 48 male Long-Evans rats (Charles River, Portage, MI) weighing approximately 300–350 g were used. Upon arrival, animals were placed in standard environment housing 1 week prior to surgery. Standard environment consisted of the animals being housed in a solitary cage (26.0 cm(w), 47.0 cm(d), and 20.3 cm(h), Alternative Design, Siloam Springs, Arkansas) with access to food and water. All animals were on a 12:12 h reversed day:night cycle. Each rat was weighed and handled for 5 min every day prior to injury. All subjects were handled and cared for under the guidelines set by the Institutional Animal Care and Use Committee of Saginaw Valley State University.

2.2. Surgical procedure of FL-SMC CCI

Animals were initially anesthetized at 5% Isoflurane and maintained for the rest of the procedure using a nose cone with 1–3% Isoflurane. Following a midline incision, animals received either a 6.0 mm craniotomy over the sensorimotor cortex portion of the left cortex 0.5 mm anterior and 4.0 mm lateral to Bregma (Kuypers and Hoane, 2010) or a sham surgery. Using an electromagnetic CCI device fitted with a 3.0 mm impactor tip, the injury was induced with 2.0 mm compression of the cortex at a velocity of 2.7 m/s (Kuypers and Hoane, 2010). The incision was then stapled together and a dime size amount of antibiotic ointment was applied to the incision. Animals were monitored until they regained movement and consciousness. Animals were then reassigned to either enriched or standard environments. Groups consisted of Sham/SE/VEH (8), Sham/EE/VEH (8), TBI/SE/VEH (8), TBI/EE/VEH (8), TBI/SE/NGF (8), and TBI/EE/NGF (8).

2.3. Enriched environments

Enriched environment housing consisted of an expansive setting (116.0 cm(w), 69.0 cm(d), and 22.0 cm(h), Alternative Design, Siloam Springs, Arkansas), a large single cage that included meaningful species-specific social interaction and behaviors. Fourteen manipulative objects or toys were routinely rearranged every day