Published in final edited form as:
Stroke. 2011 December ; 42(12): 3329–3330. doi:10.1161/STROKEAHA.111.632570.

"Won't you be my neighbor?" Deciphering the mechanisms of neuroprotection induced by social interaction

Venugopal Reddy Venna, PhD[1] and **Louise D. McCullough, MD/PhD**[1,2,3]

[1]Department of Neuroscience, University of Connecticut Health Center, Farmington, Connecticut 06030, USA

[2]MC-1840, Department of Neurology, 263 Farmington Avenue, Farmington, Connecticut 06030, USA

[3]The Stroke Center at Hartford Hospital, 85 Jefferson Street, Hartford Connecticut 06102, USA

Accumulating evidence from numerous epidemiological and pre-clinical studies has suggested that social factors can have a profound influence on physical and mental health[1–7]. People with high levels of social support or large social networks exhibit lower all-cause mortality and more rapid and extensive functional and cognitive recovery after a wide variety of pathological insults, including stroke[1–6]. In contrast, social isolation is associated with increased mortality and morbidity in patients with established vascular disease[2, 4]. Individuals who report lack of social support or isolation have an increased incidence of recurrent stroke, poorer recovery, and greater functional decline over the 5 years following a stroke compared to individuals with social support[3]. Low social support is associated with increased vascular risk even after controlling for common risk factors such as age, education, obesity, exercise, smoking, and drinking[2, 3]. Attesting to the importance of behavioral factors in stroke outcome is that these same effects can be modeled in animals[5, 8]. Social interaction improves behavioral deficits and reduces histological damage after experimental stroke, whereas isolation, even for as little as a week, enhances ischemic damage[1, 5]. The work by Karelina et al in this issue of Stroke move us closer to understanding the basic mechanisms involved in the protective effects of social interaction.

Social isolation has been defined in a myriad of ways in the literature. In general, in population based studies social isolation represents people who had poor (less than three people well enough to visit home) or limited primary informal social networks that includes friend, family or friend-neighbors[2–4, 6]. In animal studies pair housing is sufficient to elicit the beneficial effects of social integration, but physical contact is critical to obtain the full benefit[1, 5]. Although outcomes from recent clinical/epidemiological studies could not establish a link between isolation and a higher incidence of stroke, greater social support and neighborhood-level social cohesion were independently associated with reduced risk of mortality in stroke patients compared to stroke survivors exposed to pre-stroke isolation; however isolation also increased risk of depression and stress[2–4, 6], which could have their own independent effects on health. The mechanisms involved in the benefits of social support remain unclear, but increasing attention has been given to inflammatory signaling[1, 5, 6]. Epidemiological data shows higher levels of Interleukin-6 (IL-6) and hs-CRP in socially isolated individuals, although this relationship was more notable in men[6]. However, in these large epidemiological trials, numerous confounders such as compliance

Corresponding author: Louise D. McCullough, Department of Neuroscience, University of Connecticut Health Center, Farmington, Connecticut, 06030, USA. Tel:(860) 679-2271, Fax:(860) 679-1181, lmccullough@uchc.edu.

Disclosures: None

with medication, activity levels, and even differences in genetic polymorphisms that influence activation of inflammatory gene expression, must be accounted for in attributing risk. Because of these difficulties, developing animal models and exploring endogenous mechanisms by which social support improves stroke outcome in a more controlled experimental environment will help in the development of successful future therapeutic trials.

In recent years, researchers have successfully developed animal models in rodents to mimic the effects of isolation[1, 4, 7]. Isolated cohorts have increased mortality rates after stroke, more cerebral edema, and an enhanced neuroimmune response compared to pair housed animals, providing a much-needed platform to investigate the possible mechanisms that mediate the detrimental effects of social isolation[1]. Socially isolated mice have significantly higher levels of inflammatory markers, corticosterone levels and increased behavioral deficits compared to pair housed animals[1, 5]. In general many of the negative effects of psychosocial stress are thought to be mediated by increased corticosteroid levels, with activation of the hypothalamic-pituitary-adrenal (HPA) axis, and exacerbation of inflammation[5]. In contrast, the beneficial effects of positive social interactions are associated with a lowering of serum C-reactive protein concentrations, elaboration of growth factors and decreased inflammatory responses[1].

In this issue of *stroke*, Karelina and colleagues present convincing evidence for the involvement of oxytocin, a peptide hormone that modulates aspects of social behavior, in the beneficial effects of social interactions on ischemic outcome. The authors compared two cohorts of male mice that were randomly assigned to one of two different housing conditions, either socially paired (paired with an ovariectomized female) or is isolated (individually housed) in standard cages. After one week of assigned housing the males were subjected to a reversible middle cerebral artery occlusion (MCAO) and a statistically significant reduction in infarct volume in pair housed mice was found, confirming earlier work by this group. Importantly, they also found differences in oxytocin mRNA between the groups, with pair housed males showing significant elevations in oxytocin gene expression compared to isolated mice. Although the increase in oxytocin gene expression paralleled the neuroprotection, the specificity of this response was confirmed by subsequent experiments that administered an oxytocin receptor antagonist to pair housed mice. This reversed the neuroprotective response of social housing in a dose-dependent manner. Taking the opposite approach, the authors then treated socially isolated mice with exogenous oxytocin, these animals then displayed neuroprotection that was similar to that seen in pair housed mice.

Why oxytocin? Oxytocin is a mammalian neuropeptide known to play a critical role in pro-social behavior. Several previous studies have shown that exogenous oxytocin can reverse some of the detrimental effects of isolation in other models, including autonomic dysfunction and stress-induced HPA axis activation, decreasing circulating levels of adrenocorticotropin, corticosterone, and catecholamines[7] making it a promising molecular target. Both pair housing and oxytocin infusion enhanced central IL-6 levels, which have previously been shown to mediate some of the beneficial effects of affiliative housing. The levels of brain antioxidants, including glutathione peroxidase were increased by both pair housing and oxytocin infusion. However, whether this is simply an indirect effect from the reduction in infarct size is not clear from these studies. Further *in vitro* studies found that oxytocin can dose dependently inhibit LPS-induced activation in cultured microglia, although the response to LPS was not as robust as one would expect based on previous studies. It is also unclear why such a large proportion of the cultured microglia (97%) were CD11b negative, therefore this work will require confirmation. Subsequent flow cytometry confirmed the presence of oxytocin receptors on both neuronal and glial cells. Social housing significantly increased neuronal oxytocin receptor mRNA and protein expression

compared to animals that were socially isolated. Interestingly, no effects on circulating corticosterone levels were seen, suggesting that these effects may be independent of the HPA axis, or that the timing of the samples may have missed these changes. Despite these limitations, this work has identified a potentially novel signaling pathway in which pair housing induces oxytocin, leading to an enhancement of antioxidants and a decreased inflammatory response to injury and thus neuroprotection.

One major limitation of this study is that it is as yet unknown whether or not oxytocin can improve long-term functional recovery after stroke independent of its neuroprotective effects. In this study animals were pre-treated with either “social interaction” or oxytocin for a week prior to MCAO. Patients at the highest risk for social isolation may not be identified until after a stroke has occurred. Would social support be able to help this person and enhance recovery? Should we at least consider social factors in rehabilitative care plans? It is also not known if oxytocin treatment would produce similar effects in females and aged animals as these were not examined in this study. Further studies are needed to replicate these results in females, in aged animals as and in animals with comorbid illnesses such as diabetes and hypertension. Earlier work found that pair housing also benefits young females[5], but the role played by oxytocin signaling may differ due to its more prominent effects on lactation and parturition. Moreover these results need to be validated in experimental models with long-term survival and treatment initiated in post-stroke models. Unfortunately, attempts to enhance social networks in patients after myocardial ischemia have not been able to successfully mimic the beneficial effects of social interaction[8], so we must be careful in interpreting and designing future clinical studies in stroke patients. From the clinical perspective, these findings have important translational relevance as we attempt to design optimum post-stroke environments for our patients. Encouraging social interactions in aged and isolated populations could be a feasible approach for improving post-stroke outcome and reducing the substantial economic burden of stroke.

Acknowledgments

Funding Sources: LDM is supported by the NIH (RO1 5-00013) and VRV by the American Heart Association (Post Doctoral Fellowship).

References

1. Stuller KA, Jarrett B, Devries AC. Stress and social isolation increase vulnerability to stroke. Exp Neurol. 2011 Jan 28. [Epub ahead of print].
2. Barth J, Schneider S, von Kanel R. Lack of social support in the etiology and the prognosis of coronary heart disease: A systematic review and meta-analysis. Psychosom Med. 2010; 72:229–238. [PubMed: 20223926]
3. Boden-Albala B, Litwak E, Elkind MS, Rundek T, Sacco RL. Social isolation and outcomes post stroke. Neurology. 2005; 64:1888–1892. [PubMed: 15955939]
4. Clark CJ, Guo H, Lunos S, Aggarwal NT, Beck T, Evans DA, et al. Neighborhood cohesion is associated with reduced risk of stroke mortality. Stroke. 2011; 42:1212–1217. [PubMed: 21493914]
5. Craft TK, Glasper ER, McCullough L, Zhang N, Sugo N, Otsuka T, et al. Social interaction improves experimental stroke outcome. Stroke. 2005; 36:2006–2011. [PubMed: 16100018]
6. Hafner S, Emeny RT, Lacruz ME, Baumert J, Herder C, Koenig W, et al. Association between social isolation and inflammatory markers in depressed and non-depressed individuals: Results from the monica/kora study. Brain Behav Immun. 2011 Jul 2. [Epub ahead of print].
7. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry. 2003; 54:1389–1398. [PubMed: 14675803]
8. Joynt KE, O’Connor CM. Lessons from SADHART, ENRICHD, and other trials. Psychosom Med. 2005 May-Jun; 67(Suppl 1):S63–6. [PubMed: 15953805]