



Social facilitation of wound healing

Courtney E. Detillion^a, Tara K.S. Craft^a, Erica R. Glasper^a,
Brian J. Prendergast^a, A. Courtney DeVries^{a,b,*}

^aDepartment of Psychology, The Ohio State University, 01 Townsend Hall, 1885 Neil Avenue, Columbus, OH 43210 USA

^bDepartment of Neuroscience, The Ohio State University, Columbus, OH 43210 USA

Received 27 January 2003; received in revised form 15 August 2003; accepted 2 October 2003

KEYWORDS

Oxytocin; Cortisol;
Wound healing; Social
bonding;
Adrenalectomy; Stress

Summary It is well documented that psychological stress impairs wound healing in humans and rodents. However, most research effort into influences on wound healing has focused on factors that compromise, rather than promote, healing. In the present study, we determined if positive social interaction, which influences hypothalamic–pituitary–adrenal (HPA) axis activity in social rodents, promotes wound healing. Siberian hamsters received a cutaneous wound and then were exposed to immobilization stress. Stress increased cortisol concentrations and impaired wound healing in isolated, but not socially housed, hamsters. Removal of endogenous cortisol via adrenalectomy eliminated the effects of stress on wound healing in isolated hamsters. Treatment of isolated hamsters with oxytocin (OT), a hormone released during social contact and associated with social bonding, also blocked stress-induced increases in cortisol concentrations and facilitated wound healing. In contrast, treating socially housed hamsters with an OT antagonist delayed wound healing. Taken together, these data suggest that social interactions buffer against stress and promote wound healing through a mechanism that involves OT-induced suppression of the HPA axis. The data imply that social isolation impairs wound healing, whereas OT treatment may ameliorate some effects of social isolation on health.

© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

The deleterious effects of stress on immune function are well established (Kiecolt-Glaser et al., 2002). For example, wound healing, an integrative measure of organismal immune function, is impaired by exposure to both acute and chronic psychological stressors (Kiecolt-Glaser et al., 1995; Marucha et al., 1998). There are three gen-

eral stages of wound healing in humans and other animals: (a) an inflammatory stage; (b) a proliferative stage; and (c) a remodeling stage. Restraint stress (i.e. immobilization) in rodents affects the early inflammatory stage by reducing the cellular infiltration of leukocytes (i.e. macrophages), the source of proinflammatory cytokines, to the site of the wound (Padgett et al., 1998). Production of interleukin (IL)-1 β , an important mediator of wound healing (Hubner et al., 1996), is suppressed in blood samples from stressed individuals. Similarly, women reporting negative affect exhibit

*Corresponding author. Tel.: +1-614-538-9529; fax: +1-614-451-3116.

E-mail address: devries.14@osu.edu (A.C. DeVries).

elevated cortisol concentrations and suppressed IL-1 β and IL-8 production (Glaser et al., 1999). Thus, psychological stress delays wound healing, likely by reducing proinflammatory cytokine production.

The study of wound healing in rodents has elucidated the mechanisms through which stress influences aspects of wound healing (Mercado et al., 2002; Padgett et al., 1998). Chronic restraint stress reduces cutaneous wound cellularity and delays wound closure, an effect likely mediated by stress-induced increases in circulating glucocorticoid concentrations (Padgett et al., 1998). Treatment with a glucocorticoid receptor antagonist prior to restraint stress attenuates the effects of stress on wound cellularity and size (Padgett et al., 1998), and treatment with dexamethasone, a synthetic glucocorticoid, delays wound healing (Gordon et al., 1994; Hubner et al., 1996). Chronic stress or treatment with exogenous glucocorticoids also downregulates IL-1 α and IL-1 β mRNA expression at the injury site, an effect that is abolished by pretreatment with a glucocorticoid receptor antagonist (Hubner et al., 1996; Mercado et al., 2002). Stress-induced delays in wound healing are associated with an increased incidence of bacterial infection (Rojas et al., 2002). Thus, even modest delays in wound healing may have profound health consequences for individuals recovering from surgery or suffering from conditions associated with impaired wound healing (e.g. diabetes).

Opposing the deleterious effects of stress on the immune system are the beneficial effects of a supportive social environment (Coe, 1993; Cohen, 1988; Thomas et al., 1985). Individuals with access to social support exhibit improved outcome and/or recovery from a disparate array of clinical conditions, including cardiovascular disease (Grace et al., 2002), cancer (Spiegel and Sephton, 2001), systemic lupus erythematosus (Bae et al., 2001), and chronic back pain (Penttinen et al., 2002). Alternatively, loneliness, or lack of social support, is associated with impaired physical and mental health (reviewed in Cacioppo et al., 2000). Research on the immunological and neuroendocrine mechanisms of psychosocial impact on health has focused primarily on the means by which negative social interactions impair immune function. The mechanisms through which positive or beneficial social factors improve health and immune function remain unspecified (Kiecolt-Glaser et al., 2002).

Although several recent clinical and rodent studies have documented the negative effects of stress on wound healing (Kiecolt-Glaser et al.,

1995; Marucha et al., 1998; Mercado et al., 2002; Padgett et al., 1998), very little is known regarding the ability of positive social interaction to ameliorate stress effects on wound healing. Identifying and characterizing the mechanisms through which social factors promote wound healing could lead to development of therapies that facilitate healing and ultimately improve recovery from surgery or illness. The goal of the present study is to determine if positive social interactions alter immune function under stressful and non-stressful conditions. We adapted a mouse model of stress and wound healing (Padgett et al., 1998) to Siberian hamsters (*Phodopus sungorus*), which form social bonds with familiar conspecifics (Crawley, 1984). These experiments sought to test hypotheses related to the neuroendocrine mediation of immuno-enhancing effects of positive social interactions. First, we tested whether social interactions with familiar siblings mitigated deleterious effects of stress on wound healing. Next, we measured and manipulated endogenous glucocorticoids to test whether changes in glucocorticoids mediate immuno-enhancing effects of a social environment. Lastly, in light of the well-established relationship between stress, social bonding, and secretion of the hormone oxytocin (OT) (DeVries, 2002), we also assessed the contribution of OT secretion to the immuno-enhancing effects of social interactions.

2. Methods

2.1. Animals

This study was conducted in accordance with National Institutes of Health guidelines for the use of experimental animals, and the protocols were approved by the local Institutional Animal Care and Use Committee. Siberian hamsters (*P. sungorus*) were bred and raised in our laboratory at The Ohio State University (Columbus, OH, USA). Adult, sexually naïve female Siberian hamsters (2–3 months old; 22–27 g) were either individually housed or pair-housed with a female sibling from the time of weaning. All hamsters were maintained on a 14L:10D light–dark cycle and allowed ad libitum access to food and water, except during periods of restraint stress as described below.

2.2. Experimental procedures

In Experiment 1, the social preference (see Behavioral testing) of unmanipulated female hamsters

($n = 7$) for their siblings versus unfamiliar females was determined using a three-chamber apparatus. In Experiment 2, the effects of stress and social pairing on wound healing were determined using four experimental groups: Paired–Stress (PS; $n = 14$); Paired–No Stress (PNS; $n = 14$); Socially Isolated–Stress (SS; $n = 14$); and Socially Isolated–No Stress (SNS; $n = 14$). The stress animals were exposed to 2 h of restraint stress for 14 days following wounding, as described below. In Experiment 3, the effect of social pairing on cortisol concentrations was determined in pair-housed ($n = 8$ pairs) and socially isolated ($n = 11$) hamsters. Blood samples were collected at baseline, immediately following 2 h of restraint stress, and after 45 min of recovery from stress in their home cage. In Experiment 4, the role of cortisol in stress-induced suppression of wound healing was determined in four experimental groups: Adrenalectomized–Stress (ADX-S; $n = 12$); Adrenalectomized–No Stress (ADX-NS; $n = 12$); Sham-Adrenalectomized–Stress (SHAM-S; $n = 13$); and Sham-Adrenalectomized–No Stress (SHAM-NS; $n = 13$). The stressed hamsters were exposed to 2 h of restraint stress for six days following wounding, as described below. A post-stress blood sample was collected from all hamsters three days post-wounding. In Experiment 5, the effect of exogenous OT on wound healing was compared in two experimental groups: Oxytocin (OT; $n = 7$) and Vehicle Control (CTRL; $n = 8$). Hamsters in the treatment group were given injections of OT (20 mg/kg) or a vehicle for five days prior to wounding. The hamsters were exposed to 2 h of restraint stress for eight days following wounding, as described below. Blood samples were collected from a separate cohort of OT ($n = 10$) and CTRL ($n = 11$) hamsters immediately after the third day of restraint. The cortisol concentration was determined using radioimmunoassay. In Experiment 6, the effect of central administration of an OT antagonist (OTA) on wound healing was compared in two experimental groups: OTA ($n = 5$) and Vehicle Control (cerebrospinal fluid, CSF; $n = 6$). Hamsters were pair-housed with a female sibling and given injections of OTA (3 μ l) or a vehicle (artificial CSF) twice daily for two days prior to wounding. The hamsters were exposed to 2 h of restraint stress for four days following wounding, as described below.

2.3. Behavioral testing

The social preferences of experimental hamsters were evaluated using a three-chambered test apparatus. The apparatus consisted of two parallel stimulus chambers (12 \times 18 \times 28 cm), each of which was connected by a hollow tube (7.5 cm ID \times 9.0 cm in length) to a third neutral chamber (12 \times 18 \times 28 cm). The parallel chambers were occupied by either a sibling (housed with the

experimental hamster from birth) or an unrelated stranger (matched to the sibling in sex and age). The sibling and the stranger were tethered loosely in their respective chambers to limit their movement to the area of their respective home chamber. The experimental hamster was able to move freely between the three chambers. The 3 h preference tests were monitored using time-lapse video (12:1 time reduction). The tests were then scored by a single, experimentally uninformed observer, using the following ethogram: (i) duration of physical contact between the experimental hamster and the sibling or the stranger; (ii) activity, measured as the frequency of separate entries by the experimental hamster into the neutral cage; and (iii) frequency of aggression, including the incidence of threats, attacks, or fights.

2.4. Wounding procedure

Experimental hamsters were anesthetized with isoflurane in oxygen-enriched air. A 3 \times 3 cm patch of fur was shaved on the dorsal surface and cleansed with betadine (Purdue Frederick, Stamford, CT). Dorsal, mid-scapular cutaneous wounds were produced using a sterile 3.5 mm dermal punch biopsy tool (Miltex Instruments, Bethpage, NY).

2.5. Analysis of wounds

Each day, beginning with the day of wounding, the hamsters were briefly anesthetized (<30 s) with isoflurane in oxygen-enriched air and the wound site was photographed using a digital camera. Each photograph included a standard-sized circle (3.5 mm ID) that was placed on the skin close to the wound. The wound size for each hamster was determined using Canvas 8.0 (Deneba Systems, Miami, FL) and expressed as the ratio of wound area (in pixels) to the area (in pixels) of the standard circle in the photograph.

2.6. Restraint stress

In each experiment, restraint stress was initiated 24 h post-wounding. The stress consisted of inserting hamsters into small Plexiglas tubes (3 cm ID, 10 cm in length) for 2 h per day for 14 consecutive days. The restraint tubes allowed for minimal, confined movement. The time of day that the stress was administered, 2–4 h prior to onset of the dark cycle, remained constant throughout the study. Hamsters in the unstressed conditions remained undisturbed in their home cages.

2.7. Adrenalectomy procedure

Experimental hamsters were anesthetized with isoflurane in oxygen-enriched air. A dorsomedial incision provided a clear view of the adrenal gland. To remove the adrenal gland, gentle suction was applied to the gland while it was carefully teased away from the kidney. The adrenal gland was inspected upon removal to ensure that the capsule was intact. In the control (SHAM) adrenalectomy procedure, the adrenal glands were visualized, but not disturbed. Following surgery, ADX hamsters were provided with a bottle of tap water and a bottle containing 3% NaCl solution. Both SHAM and ADX hamsters were given 2.0 ml IP injections of sterile isotonic saline daily starting with the day of surgery and continuing throughout the duration of the experiment. Surgeries were performed 48 h prior to wounding.

2.8. Determination of blood cortisol concentrations

Blood samples (50 μ l) were collected from the periorbital sinus over three consecutive days (2–5 h before the onset of darkness). Baseline samples were drawn on day 1, approximately 90 min prior to restraint stress. A second sample (Stress) was collected on day 2 at the conclusion of the 2 h restraint stress. The last sample (Recovery), taken on day 3, was collected 45 min after the hamsters were removed from the restraint tubes and returned to their home cages. Blood samples were centrifuged at 6 °C for 20 min at 2500g. The plasma was collected and stored at –70 °C. Cortisol concentrations were determined in duplicate samples in a single assay using a 125 I radioimmunoassay kit (Diagnostic Products Corp., Los Angeles, CA).

2.9. Oxytocin administration

The experimental hamsters received IP injections of oxytocin (Sigma-Aldrich, St. Louis, MO) at a dose of 20 mg/kg. The OT was dissolved in saline and administered at a dose of 1 ml/kg. Control hamsters received IP injections of isotonic saline at a volume of 1 ml/kg. Injections were given once per day for five days prior to the onset of restraint stress.

2.10. Oxytocin antagonist administration

The oxytocin antagonist (desGly-NH₂-d(CH₂)₅[D-Tyr²,Thr⁴]OVT^a) was generously donated by Dr. Maurice Manning (Medical College of Ohio, Toledo, OH, USA). Three days prior to wounding, the hamsters were anesthetized, their skull surface exposed, and a small hole drilled through the skull

(–0.1 anterior/posterior, –0.9 medial/lateral from bregma). A 26 gauge stainless-steel guide cannula cut 2.35 mm below the pedestal (Plastics One Inc, Roanoke, VA) was implanted, via a stereotaxic apparatus, into the right lateral cerebral ventricle. The cannula was secured to the surface of the skull with cranioplastic cement. Hamsters received a 3 μ l injection of OTA (0.05 μ g) twice daily beginning the evening prior to wounding. At the conclusion of the experiment, the patency and placement of the cannula were verified by post-mortem injection of dilute India ink through the cannula.

2.11. Statistical analyses

Analysis of variance (ANOVA) for repeated measures was used to analyze the wound size. Post hoc comparisons were conducted using Fisher's PLSD test. Social preferences were determined using a paired *t*-test to compare time spent in physical contact with the sibling versus the unfamiliar stimulus hamster. Cortisol concentrations in Experiment 3 exhibited unequal variance between treatment groups and were compared using a Wald–Wolfowitz rank test. Effects were considered statistically significant if $P \leq 0.05$.

3. Results

3.1. Experiment 1

The experimental hamsters demonstrated a strong preference for their sibling versus an unfamiliar stranger ($t_6 = 3.41$; $P < 0.05$). The experimental hamsters spent $48.84 \pm 6.55\%$ of the test time in the cage of the sibling, while only spending $9.27 \pm 1.80\%$ of the time in the stranger's cage. The experimental hamsters were in physical contact with the sibling $42.96 \pm 9.65\%$ of the time they were in the partner's chamber. In contrast, only $8.42 \pm 3.07\%$ of the time in the stranger's cage was spent in physical contact.

3.2. Experiment 2

There was a significant effect of day ($F(14, 658) = 300.88$; $P < 0.05$), housing ($F(1, 47) = 16.97$; $P < 0.05$), and stress ($F(1, 47) = 7.57$; $P < 0.05$) on wound healing. Wounds were significantly larger in the SI–Stress group compared to the P–Stress group on days 1–3, 5–8, 10, and 11 ($P < 0.05$; Fig. 1a). The SI–Stress group had significantly larger wounds than the SI–No stress group on days 2 and 5–8 ($P < 0.05$; Fig. 1a). At no time point

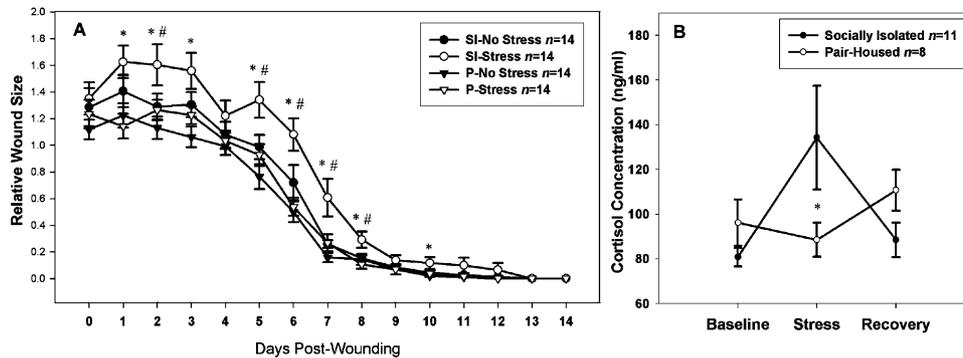


Fig. 1. Social isolation impairs wound healing and exacerbates cortisol responses to stress. (a) There was a significant effect of day, housing, and stress on wound healing. Two hours of daily restraint stress impaired wound healing in socially isolated (SI) hamsters, but not pair-housed (P) hamsters. The SI–Stress group had significantly larger wounds than the SI–No stress group on days 2 and 5–8 (#, $P < 0.05$). Wounds were significantly larger in the SI–Stress group than the paired P–Stress group on days 1–3, 5–8, and 10 (*, $P < 0.05$). Stress had no effect on wound size in P hamsters ($P > 0.05$). Data ($n = 14$ /group) were analyzed using ANOVA for repeated measures followed by post hoc comparisons using Fisher’s test. (b) Cortisol concentrations (mean \pm SEM) were significantly greater in SI than P hamsters immediately following 2 h of restraint stress, but not at baseline or following a 45 min recovery. Although there was no significant overall effect of housing or sample (baseline, immediately post-stress, recovery) on cortisol concentration, there was a significant interaction between sample and housing condition. Cortisol data were analyzed using the Wald–Wolfowitz rank test. An asterisk (*) indicates statistical significance ($P < 0.05$) between P and SI animals.

were there significant differences in wound size between the P–Stress and P–No stress groups, or either of the Paired groups and the SI–No stress group (Fig. 1a).

3.3. Experiment 3

Based on the results from Experiment 2, we hypothesized that social interaction decreases hypothalamic–pituitary–adrenal (HPA) axis reactivity and we predicted that socially isolated hamsters would exhibit a greater elevation in cortisol concentration during stress and subsequently take longer to return to their baseline concentrations of cortisol following a stressor. Although there was no significant overall effect of housing ($F(1, 17) = 0.114$; $P > 0.05$) or time of sampling (baseline, immediately post-stress, recovery: $F(2, 34) = 1.10$; $P > 0.05$) on cortisol concentration, there was a significant interaction between sample and housing condition ($F(2, 56) = 3.56$; $P < 0.05$). Post hoc analyses indicated unequal variance between treatment groups; therefore, plasma cortisol concentrations were compared using a Wald–Wolfowitz rank test. Cortisol concentrations were significantly higher immediately post-stress in the socially isolated hamsters relative to the pair-housed hamsters ($P < 0.05$; Fig. 1b), but the two experimental groups did not differ at baseline or recovery ($P > 0.05$).

3.4. Experiment 4

Based on the outcomes of Experiments 2 and 3, we hypothesized that the suppression of cortisol concentration in pair-housed hamsters is the mechanism responsible for the expedited wound healing, and we predicted that the removal of the main source of cortisol from the body would be as beneficial as having a partner present during the healing process. Although there was no overall significant effect of treatment on wound size ($F(3, 46) = 2.32$; $P = 0.08$), there was a significant effect of day ($F(6, 276) = 89.64$; $P < 0.01$) and an interaction between treatment and day ($F(18, 276) = 2.23$; $P < 0.01$) on wound size (data not shown). Post hoc analyses revealed that wound sizes were larger in the SHAM-S group than both the ADX-S and ADX-NS groups on days 2, 3, and 4. The SHAM-S wounds were significantly larger than the SHAM-NS wounds on day 2. There was no significant difference in wound sizes of the ADX-S and ADX-NS groups at any time point. Collectively, these data suggest that stress-induced cortisol secretion inhibits wound healing.

3.5. Experiment 5

Based on the results from Experiments 2 and 4, we hypothesized that OT secretion was increased by the presence of a sibling, and we predicted that treatment with exogenous OT would decrease

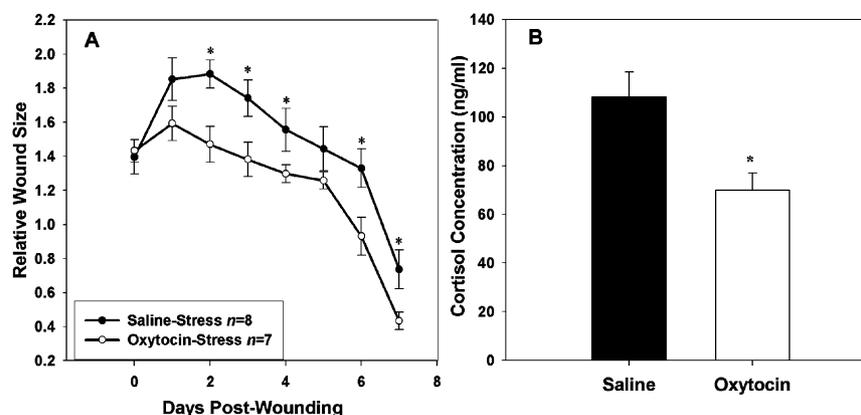


Fig. 2. Oxytocin (OT) facilitates wound healing and suppresses the HPA axis in stressed hamsters. (a) Female hamsters injected IP with exogenous OT exhibited significantly smaller wounds than females treated with the vehicle on days 2–4, 6, and 7. Both experimental groups were subjected to 2 h daily restraint stress. Data were analyzed using ANOVA and are presented as mean \pm SEM. An asterisk (*) indicates statistical significance at $P < 0.05$ between the OT and control groups. (b) Cortisol concentrations were significantly lower in hamsters injected with OT than those injected with the vehicle control (saline). Data are presented as mean \pm SEM.

wound size and suppress the release of cortisol during periods of stress. Female hamsters injected with OT exhibited significantly smaller wounds than females treated with the vehicle on days 2–4, 6, and 7 ($F(1, 13) = 7.73$; $P < 0.05$; Fig. 2a). Furthermore, stress-induced cortisol concentrations were significantly lower in OT than CTRL animals ($t_{19} = 3.02$, $P < 0.01$; Fig. 2b).

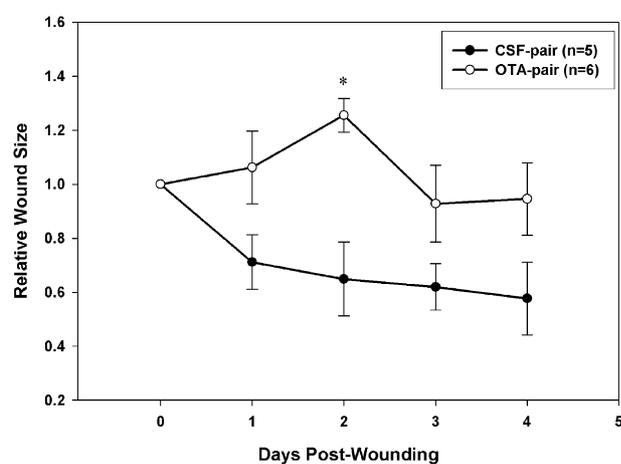


Fig. 3. Oxytocin antagonist (OTA) impairs wound healing. Female hamsters injected ICV with OTA exhibited significantly larger wounds than females treated with the CSF vehicle. Both experimental groups were pair-housed. Data ($n = 5–6$ /group) were analyzed using ANOVA for repeated measures followed by post hoc comparisons using Fisher's test and are presented as mean \pm SEM. An asterisk (*) indicates statistical significance at $P < 0.05$ between the OTA and the CSF control group.

3.6. Experiment 6

Based on the results from Experiments 5, we hypothesized that OT secretion was increased by the presence of a sibling, and we predicted that treatment with OTA would increase wound size. Because wound size on day 0 was significantly different between groups, the data are presented and analyzed as a ratio of day X /day 0. There was a significant effect of treatment ($F(1, 9) = 7.87$; $P < 0.05$) and day ($F(3, 27) = 3.05$; $P < 0.05$) on wound size. Socially paired hamsters injected with OTA exhibited significantly larger wounds than females treated with CSF on day 2 (Fig. 3).

4. Discussion

The results of this study provide evidence that positive social interactions improve wound healing. Individually housed hamsters exposed to chronic stress induced by daily restraint exhibited increased cortisol concentrations and larger wounds relative to unstressed, socially isolated hamsters. Secretion of cortisol may be responsible for stress-induced delays in healing because artificially reducing endogenous corticosteroid concentrations, achieved via adrenalectomy, ameliorated the effects of restraint stress on wound healing. Thus, stress exposure increased wound size in SHAM-ADX, but not in ADX hamsters. Corticosteroid responses to restraint stress also were suppressed by pairing hamsters with a sibling. Although social housing did not affect baseline serum cortisol concentrations, pair-housed hamsters had significantly lower cortisol

concentrations relative to socially isolated hamsters upon removal from restraint. Indeed, restraint stress significantly increased cortisol concentrations in socially isolated hamsters but not in pair-housed hamsters. These data suggest that social housing provides a buffer against stress-induced activation of the HPA axis. Furthermore, social housing ameliorated the effects of stress on wound healing. There were no significant differences in wound size between pair-housed animals subjected to restraint stress and those maintained under non-stressful conditions.

In humans, social support significantly alters cardiovascular and corticosteroid responses to laboratory stressors (Thorsteinsson and James, 1999). In common with humans, Siberian hamsters form social bonds that may influence reactivity to stressors and ultimately affect health. Socially bonded male Siberian hamsters defend territories and provide parental care to their young (Castro and Matt, 1997). Disruption of a male–female bond results in a persistent increase in basal serum cortisol concentrations and behavioral alterations (Castro and Matt, 1997; Crawley, 1984). In the current study, we demonstrated that female Siberian hamsters likewise exhibit a significant social preference for a female sibling. Social preference is often used as an index of pair-bonding (Carter, 1998) and has been demonstrated between same-sex individuals in monogamous prairie voles (*Microtus ochrogaster*; DeVries et al., 1997). Socially bonded hamsters are less responsive than individually housed hamsters to restraint stress, but more responsive to stress involving an intruder into the home territory (Castro and Matt, 1997). Thus, it appears that social suppression of the HPA axis is stimulus dependent.

An extensive clinical and experimental literature suggests that social interactions can have a profound effect on health (Cohen, 1988; Uchino et al., 1996). However, little is known regarding the mechanisms through which social support in humans and affiliative behaviors in other animals achieve these beneficial effects. In the present study, we tested the hypothesis that OT-induced suppression of the HPA axis provides a mechanism by which social interaction may facilitate wound healing. OT is a peptide hormone involved in the regulation of lactation and parturition, but OT also is released in response to physical contact (Gimpl and Fahrenholz, 2001; Uvnas-Moberg, 1997) and is correlated positively with social behavior (Haller et al., 1996). Furthermore, HPA axis hypo-responsivity is common in natural physiological states associated with high concentrations of OT, such as lactation (reviewed in

DeVries, 2002). Exogenous OT also suppresses the HPA axis under a wide range of physiological and pharmacological conditions (Chiodera et al., 1991; Petersson et al., 1999). Namely, in the present study, hamsters that were treated with exogenous OT had lower stress-induced cortisol concentrations than vehicle-treated animals. OT-treated animals also had smaller wounds relative to vehicle-treated hamsters at several time points. In contrast, treating pair-housed hamsters with OTA increased wound size. Thus, it appears that OT, in common with social housing, buffers against stress-induced delays in wound healing.

Collectively, these data suggest that stress impairs wound healing via a mechanism that involves increased HPA activity. In contrast, social housing decreases HPA reactivity to restraint stress and improves wound healing. A likely mechanism through which social housing influences stress responsivity is the release of OT during social interaction. To illustrate, treatment with exogenous OT suppresses HPA reactivity to stress and improves wound healing by decreasing cortisol concentrations during the inflammatory stage of wound healing. Ultimately, a stress-induced delay in wound healing can compromise health; one mechanism by which this may occur is increased incidence of opportunistic infection (Rojas et al., 2002). Such infections could have particularly disastrous consequences for immuno-compromised individuals such as diabetics, cancer patients, AIDS patients, and organ transplant recipients (Becker, 1986; Hollenbeak et al., 2001). Thus, socially isolated individuals, particularly those with concomitant medical complications, may be most susceptible to stress-induced impairment of wound healing and ultimately at greater risk for wound infection. Identification of OT as a potential mechanism responsible for social suppression of HPA activity and improvement of wound healing suggests a therapeutic target which, if developed, may lead to improved wound healing and amelioration of other stress-related illnesses.

Acknowledgements

This work is supported by a seed grant from The Ohio State University Stress and Wound Healing Center. We would like to thank Dr. John Sheridan and Ray Tseng for the technical assistance. We also would like to thank Dr. Maurice Manning (Medical College of Ohio, Toledo, OH) for providing the OTA antagonist and suggestions on dose and administration regimen.

References

- Bae, S.C., Hashimoto, H., Karlson, E.W., Liang, M.H., Daltroy, L.H., 2001. Variable effects of social support by race, economic status, and disease activity in systemic lupus erythematosus. *J. Rheumatol.* 28, 1245–1251.
- Becker, G.D., 1986. Identification and management of the patient at high risk for wound infection. *Head Neck Surg.* 8, 205–210.
- Cacioppo, J.T., Ernst, J.M., Burleson, M.H., McClintock, M.K., Malarkey, W.B., Hawkley, L.C., Kowalewski, R.B., Paulsen, A., Hobson, J.A., Hugdahl, K., Spiegel, D., Berntson, G.G., 2000. Lonely traits and concomitant physiological processes: the MacArthur social neuroscience studies. *Int. J. Psychophysiol.* 35, 143–154.
- Carter, C.S., 1998. Neuroendocrine perspectives on social attachment and love. *Psychoneuroendocrinology* 23, 779–818.
- Castro, W.L., Matt, K.S., 1997. Neuroendocrine correlates of separation stress in the Siberian dwarf hamster (*Phodopus sungorus*). *Physiol. Behav.* 61, 477–484.
- Chiodera, P., Salvarani, C., Bacchi-Modena, A., Spallanzani, R., Cigarini, C., Alboni, A., Gardini, E., Coiro, V., 1991. Relationship between plasma profiles of oxytocin and adrenocorticotrophic hormone during suckling or breast stimulation in women. *Horm. Res.* 35, 119–123.
- Coe, C.L., 1993. Psychosocial factors and immunity in nonhuman primates: a review. *Psychosom. Med.* 55, 298–308.
- Cohen, S., 1988. Psychosocial models of the role of social support in the etiology of physical disease. *Health Psychol.* 7, 269–297.
- Crawley, J.N., 1984. Evaluation of a proposed hamster separation model of depression. *Psychiatry Res.* 11, 35–47.
- DeVries, A.C., 2002. Interaction among social environment, the hypothalamic–pituitary–adrenal axis, and behavior. *Horm. Behav.* 41, 405–413.
- DeVries, A.C., Gerber, J.M., Richardson, H.N., Moffatt, C.A., Demas, G.E., Taymans, S.E., Nelson, R.J., 1997. Stress affects corticosteroid and immunoglobulin concentrations in male house mice (*Mus musculus*) and prairie voles (*Microtus ochrogaster*). *Comp. Biochem. Physiol. A Physiol.* 118, 655–663.
- Gimpl, G., Fahrenholz, F., 2001. The oxytocin receptor system: structure, function, and regulation. *Physiol. Rev.* 81, 629–683.
- Glaser, R., Rabin, B., Chesney, M., Cohen, S., Natelson, B., 1999. Stress-induced immunomodulation: implications for infectious diseases? *J. Am. Med. Assoc.* 281, 2268–2270.
- Gordon, C.B., Li, D.G., Stagg, C.A., Manson, P., Udelsman, R., 1994. Impaired wound healing in Cushing's syndrome: the role of heat shock proteins. *Surgery* 116, 1082–1087.
- Grace, S.L., Abbey, S.E., Shnek, Z.M., Irvine, J., Franche, R.L., Stewart, D.E., 2002. Cardiac rehabilitation I: review of psychosocial factors. *Gen. Hospital Psychiatry* 24, 121–126.
- Haller, J., Makara, G.B., Barna, I., Kovacs, K., Nagy, J., Vecsernyes, M., 1996. Compression of the pituitary stalk elicits chronic increases in CSF vasopressin, oxytocin as well as in social investigation and aggressiveness. *J. Neuroendocrinol.* 8, 361–365.
- Hollenbeak, C.S., Alfrey, E.J., Souba, W.W., 2001. The effect of surgical site infections on outcomes and resource utilization after liver transplantation. *Surgery* 130, 388–395.
- Hubner, G., Brauchle, M., Smola, H., Madlener, M., Fassler, R., Werner, S., 1996. Differential regulation of pro-inflammatory cytokines during wound healing in normal and glucocorticoid-treated mice. *Cytokine* 8, 548–556.
- Kiecolt-Glaser, J.K., Marucha, P.T., Malarkey, W.B., Mercado, A.M., Glaser, R., 1995. Slowing of wound healing by psychological stress. *Lancet* 346, 1194–1196.
- Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., Glaser, R., 2002. Psychoneuroimmunology: psychological influences on immune function and health. *J. Consult. Clin. Psychol.* 70, 537–547.
- Marucha, P.T., Kiecolt-Glaser, J.K., Favagehi, M., 1998. Mucosal wound healing is impaired by examination stress. *Psychosom. Med.* 60, 362–365.
- Mercado, A.M., Padgett, D.A., Sheridan, J.F., Marucha, P.T., 2002. Altered kinetics of IL-1 alpha, IL-1 beta and KGF-1 gene expression in early wounds of restrained mice. *Brain Behav. Immun.* 16, 150–162.
- Padgett, D.A., Marucha, P.T., Sheridan, J.F., 1998. Restraint stress slows cutaneous wound healing in mice. *Brain Behav. Immun.* 12, 64–73.
- Penttinen, J., Nevala-Puranen, N., Airaksinen, O., Jaaskelainen, M., Sintonen, H., Takala, J., 2002. Randomized controlled trial of back school with and without peer support. *J. Occup. Rehabil.* 12, 21–29.
- Petersson, M., Hulting, A.L., Uvnas-Moberg, K., 1999. Oxytocin causes a sustained decrease in plasma levels of corticosterone in rats. *Neurosci. Lett.* 264, 41–44.
- Rojas, I.G., Padgett, D.A., Sheridan, J.F., Marucha, P.T., 2002. Stress-induced susceptibility to bacterial infection during cutaneous wound healing. *Brain Behav. Immun.* 16, 74–84.
- Spiegel, D., Sephton, S.E., 2001. Psychoneuroimmune and endocrine pathways in cancer: effects of stress and support. *Semin. Clin. Neuropsychiatry* 6, 252–265.
- Thomas, P.D., Goodwin, J.M., Goodwin, J.S., 1985. Effect of social support on stress-related changes in cholesterol level, uric acid level, and immune function in an elderly sample. *Am. J. Psychiatry* 142, 735–737.
- Thorsteinsson, E., James, J., 1999. A meta-analysis of the effects of experimental manipulations of social support during laboratory stress. *Psychol. Health* 14, 869–886.
- Uchino, B.N., Cacioppo, J.T., Kiecolt-Glaser, J.K., 1996. The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychol. Bull.* 119, 488–531.
- Uvnas-Moberg, K., 1997. Oxytocin linked antistress effects—the relaxation and growth response. *Acta Physiol. Scand. Suppl.* 640, 38–42.