Published in final edited form as:

Psychosom Med. 2011 January ; 73(1): 67–74. doi:10.1097/PSY.0b013e3182002116.

Modeling Social Influences on Human Health

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Abstract

Social interactions have long-term physiological, psychological and behavioral consequences. Social isolation is a well recognized but little understood risk factor and prognostic marker of disease, and can have profoundly detrimental effects on both mental and physical well-being, particularly during states of compromised health. In contrast, the health benefits associated with social support (both reduced risk and improved recovery) are evident in a variety of illnesses and injury states; however, the mechanisms by which social interactions influence disease pathogenesis remain largely unidentified. The substantial health impact of the psychosocial environment can occur independently of traditional disease risk factors and is not accounted for solely by peer-encouraged development of health behaviors. Instead, social interactions are capable of altering shared pathophysiological mechanisms of multiple disease states in distinct measurable ways. Converging evidence from animal models of injury and disease recapitulates the physiological benefits of affiliative social interactions and establishes several endogenous mechanisms (inflammatory signals, glucocorticoids and oxytocin) by which social interactions influence health outcomes. Taken together, both clinical and animal research are undoubtedly necessary in order to develop a complete mechanistic understanding of social influences on health.

Keywords

Social interaction; health; experimental models; oxytocin

Social influences on health

Social interactions shape humans from early development through senescence and have a strong impact on many aspects of physiology and behavior. Indeed, social interaction is essential for proper cognitive, affective and behavioral development (1). Among adults, the social environment remains an important determinant of health and well being; ample evidence suggests that positive social support accelerates and improves patient recovery from cancer, cerebrovascular and cardiovascular disease (CVD), atherosclerosis, and other chronic diseases with an inflammatory component (2–5). This has led to a substantial interest in the capacity to which the social environment affects physiological systems, particularly during health challenges. The benefits of a positive social environment are particularly salient in chronic disease states, in which emotional social support can be perceived as being equally or more important than instrumental and informational support

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Conflict of interest: All authors declare that they have no conflicts of interest in publishing this manuscript

(6). In contrast, social isolation and loneliness can have profoundly detrimental effects on mental and physical health (7). While this observation is not novel in the medical community (8–10), it has only relatively recently begun to gain momentum in both clinical and animal research. The addition of evaluating patients' social, along with cognitive and physical states, while not yet considered common practice, is gaining acceptance in hospitals and clinics worldwide (11–12); however, despite growing evidence implicating the social environment as a modifying factor in disease outcomes, little is known regarding the mechanisms through which psychosocial factors influence disease pathogenesis. Converging evidence from experimental research suggests that socially isolated animals mount a quantitatively and qualitatively different pathophysiological response to disease and physical trauma compared to socially housed animals. Moreover, the benefits of social housing in animal models are remarkably consistent with clinical findings, and are evident in a diverse set of disease and injury models. The aim of this review is to further illustrate the need for integrative clinical and experimental research that encompasses a more complete understanding of the qualitative and quantitative consequences of social experiences on disease physiology.

Chronic diseases such as cardiovascular and cerebrovascular disease, diabetes, cancer, and autoimmune disorders accounted for 70% of all deaths in the United States in 2005 (13). A substantial research effort has elucidated a number of risk factors (e.g. smoking, alcohol consumption, high blood pressure, cholesterol, etc) that are common across most chronic disease states, as well as identified causal relationships and mechanisms by which these factors influence disease onset and outcome. Interestingly, even after statistically controlling for these risk factors, there still exists substantial inter-individual variability in susceptibility to disease and recovery. This naturally occurring variability can be accounted for in part by an additional class of risk factors: psychological stress (including social isolation or perceived lack of social support), that is predictive of disease outcome independently of other traditional risk factors (14–15). Importantly, the impact of the social environment is not only evident during the course of disease, but also influences the development of potentially debilitating consequences such as chronic pain, long-term physical disability, and psychological distress such as anxiety/depression (16).

A prevailing hypothesis is that social support improves health by promoting healthy behaviors. Indeed, social support is associated with better medical compliance, increased physical exercise, improved nutrition and low-to-moderate tobacco and alcohol consumption (17). While it is not surprising that social and peer support increases the likelihood of engaging in health behaviors (whether because of the pressure to conform to social norms or a potential increase of tangible resources), statistically controlling for these behavioral changes indicates that the benefits of social support remain substantial (15,18–19). The major implication of these findings is the need to identify an endogenous physiological mechanism through which social behaviors influence physiological parameters that have important health implications.

To date, it has been difficult to definitively establish a causal relationship between psychosocial factors and disease among the clinical population, however, a number of successful longitudinal studies have identified social isolation as a predictor of physiological measures that are known risk-factors for disease, including onset of CVD, even 20 years following initial assessment (19–20). Indeed, childhood social isolation is associated with a greater number of CVD and stroke risk factors, including high body mass index, high blood pressure and cholesterol, and low oxygen consumption in adulthood (19). These data demonstrate that the relationship between social isolation and disease is not strictly correlational; rather, early experiences of social isolation can predict the development of risk factors well into adulthood.

Two important questions emerge in light of these studies. (1) What are the shared pathophysiological features among the disease states that are influenced by social experiences, and (2) in what way are they modifiable by the psychosocial environment? Inflammatory processes represent one common mechanism of disease that underlies the multiple pathophysiologies described in this review. Indeed, chronic inflammation increasingly ranks as an important risk factor for stroke and CVD, as well as many cancers, Alzheimer's disease and major depression disorder (21–25). For example, patients presenting with systemic inflammation, such as systemic lupus erythematosus and rheumatoid arthritis, have a 4–10 fold increased risk of developing CVD (reviewed in 26). This relationship is particularly evident in coronary and cerebral ischemia, as inflammation is relevant both as an indicator of an underlying cause (i.e. atherosclerosis 27) and as an important mediator (22), rather than just a biomarker of ischemia. As such, chronic inflammation has become a main focus for monitoring and prevention of stroke and CVD. In particular, systemic levels of acute phase proteins such as C-reactive protein (CRP) and proinflammatory cytokines (primarily interleukin 6; IL-6) predict the risk and prognosis of stroke and CVD (21,28). Importantly, circulating CRP and IL-6 levels are reduced in patients with sufficient social support, thus presenting one mechanism by which social experiences could influence stroke and CVD (29–30); however, the intermediate signal that interprets and translates the social environment into an altered inflammatory response remains unknown.

One signal that may serve to transduce social experiences into an altered physiology is oxytocin (OT). OT is a neuropeptide that is released during social interactions. Exogenous OT administration has been shown to increase pro-social behaviors in humans, including the ability to interpret emotions of others (31), interpersonal communication and social approach behavior (32). Anxiolytic properties of OT are also evident in clinical studies. Indeed, a particularly robust finding in the clinical literature is the relationship between endogenous OT (which is elevated during lactation) and stress hyporesponsiveness. Lactating and nursing women have attenuated stress responses (33) and lower blood pressure (34) compared to non-lactating controls. Moreover, this stress buffering effect of social interaction can be mimicked with exogenous OT administration (35). Taken together, the role of OT in mediating social behaviors as well as stress physiology makes it an attractive potential endogenous signaling mechanism by which social behaviors influence health.

Overall, the precise mechanisms through which psychosocial factors influence the pathophysiological response to disease remain unknown because (1) the relevant clinical studies are inconsistent in the way they define social support and often don't distinguish between the various types of social support (i.e. functional, emotional, informational, etc) and importantly (2) the manipulations necessary to establish a causal link between social support and health outcomes cannot be conducted ethically in humans. On the other hand, environmental factors such as social housing are easily modifiable in laboratory animals and produce reliable and quantifiable physiological effects, and as such can be used to establish causation as well as to allow extensive characterization of the physiological mechanisms underlying social influences on disease.

Animal models of social influences on disease outcome

As the impact of social housing conditions (i.e. single vs. pair/group housing) on rodent welfare gains attention, it is becoming increasingly evident that for some species, social isolation is a profound psychological stressor. Chronic individual housing of rodents induces symptoms of “isolation syndrome” including depressive-like behavior (36–37), stress and anxiety-like behaviors (38–39), as well as aggression (40). In addition, the physiological

consequences of social isolation include autonomic dysregulation (41), altered metabolism, heart rate, and core body temperature (42–44), and suppression of adult neurogenesis (45). Many of the negative consequences of social isolation are ameliorated simply by manipulating social housing conditions (46–48).

Existing animal models of disease, in particular rodent models of ischemia, atherosclerosis, neuropathic pain, and wound healing – disease states well known to be influenced by social factors in the clinical population – are all sensitive to social manipulations. As such, a growing body of experimental literature has provided evidence that the behavioral and physiological consequences of social isolation include increased susceptibility to disease, delayed wound healing, and a disruption of functional recovery following trauma or injury. Importantly, there is a high degree of agreement among the clinical and emerging rodent data on the positive effects of social interaction on the pathogenesis of these disease states, and the implications of these data are now being extended to study the mechanisms by which social factors influence disease pathophysiology (table 1).

Cerebral Ischemia

Social housing has been shown to significantly affect measures of cerebral ischemia outcome in a series of studies employing well-characterized mouse models of focal (stroke) and global (cardiac arrest) cerebral ischemia (49–51). To study social influences on ischemia outcome, mice are housed singly (socially isolated), or are socially housed in same-sex groups or paired with an ovariectomized female. Using experimental stroke models: unilateral middle cerebral artery occlusion (MCAO) and cardiac arrest/cardiopulmonary resuscitation (CA/CPR), our lab (49–52) has reported that the social housing condition is a strong determinant of the pathophysiological response and long-term survival following experimental stroke. Mice housed in pairs are 60% more likely to survive 7 days following the ischemic damage (51). Moreover, social housing reduces cell death, brain water content (edema) and infarct size relative to social isolation in both the stroke and cardiac arrest models of ischemia (49–53). In addition, experimental stroke in rodents produces functional deficits similar to those that occur following a clinical stroke, namely a reduction of coordinated limb use contralateral to the affected hemisphere followed by a reduction of overall mobility depending on stroke severity. Social housing reduces post-ischemic functional deficits and accelerates recovery of locomotor activity relative to social isolation (50,52).

Neuropathic Pain

Social interaction is further implicated as a modulating factor of the development of neuropathic pain, which occurs as a result of a dysfunction or injury to the central nervous system. Neuropathic pain is modeled in mice by inducing a peripheral nerve injury in the hind limb. Subsequent development of neuropathic pain is then measured as paw withdrawal in response to an innocuous stimulus (small filaments applied to the lateral side of the paw). Following nerve injury, socially housed mice exhibit a significant increase in paw withdrawal thresholds relative to socially isolated mice, indicating a reduction of neuropathic pain response (54). Importantly, depressive-like behavior, a common consequence of chronic pain, is also reduced in the socially housed animals (55). Taken together with the behavioral data from the ischemia studies, these data indicate that the influence of social interaction extends beyond the course of central nervous system injury and continues to affect the development of arguably the most debilitating consequences of CNS damage including functional deficits, chronic pain and depression.

Wound Healing

Additional extensive insight into the neurobiological correlates of social behavior and pathophysiology is possible through comparison of closely related rodent species that exhibit different social systems. For example, the socially monogamous *Peromyscus californicus* mice exhibit a strong tendency toward forming long-lasting bonds with a mate, while the closely related *Peromyscus leucopus* exhibit behaviors consistent with a polygynous social system and tend to be solitary in nature (56–57). These animals provide an excellent natural model for studying the impact of social structure and the accompanying physiological and behavioral correlates on health outcomes. As such, *Peromyscus californicus* and *leucopus* were recently used to establish the finding that the health-promoting benefits of social interaction are further evident in non-CNS injuries with an inflammatory component (58). In order to assess social influences on the rate of wound healing, small (3.5 mm diameter) wounds are created using a punch biopsy tool on the dorsum. The wounds are then photographed and measured daily for determination of healing rate. Interestingly, social housing only facilitated wound healing among the monogamous *Peromyscus californicus*, whereas the healing rate among the polygynous *Peromyscus leucopus* remained similar between socially housed and isolated mice (58). Likewise, social interaction among Siberian hamsters, which form social bonds with familiar conspecifics, improves wound healing (59). Taken together, these data suggest that the ability to form social bonds significantly affects the extent to which social interactions influence health outcomes.

Mechanisms of social influences on health

Inflammation

The immune system actively regulates and sustains a state of homeostasis under normal physiological conditions. However, following trauma, the organism enters a pro-inflammatory and pro-thrombotic state (60). This state of systemic inflammation involves the activation of macrophages and T cells, the release of soluble factors such as cytokines and chemokines, leukocyte extravasation and the upregulation of adhesion molecules, among a multitude of other immune effectors (60). Whereas acutely this is a coordinated adaptive response intended to restore homeostasis and remove pathogens and dead/dying cells, there are serious long-term consequences associated with tipping the balance toward a chronic proinflammatory state.

Thus, social modulation of inflammatory processes represents a plausible link between social interactions and health. Indeed, a particularly robust finding in the clinical literature is an inverse relationship between social support and circulating CRP and IL-6 in otherwise healthy individuals (29–30). It follows that increased stroke and CVD morbidity and mortality rates in socially isolated individuals may be a reflection of elevated chronic low-grade inflammation (61).

Animal models provide evidence that the social housing influence on disease is accompanied by altered systemic and neuroinflammatory responses. In parallel to clinical findings, circulating IL-6 is reduced in socially housed mice following experimental stroke (51) or cardiac arrest (53). Moreover, the circulating concentration of CRP, which is induced by IL-6, is similarly reduced following MCAO in socially housed animals and the reduction of both markers is accompanied by smaller infarcts and improved functional recovery (50,52). Interestingly, while circulating IL-6 is reduced in socially housed mice, the same group of animals exhibits increased brain IL-6 protein concentrations (52). These data are consistent with findings that increased central IL-6 is neuroprotective in stroke models (62–63). Indeed, central pretreatment of socially housed animals with a neutralizing antibody to IL-6 eliminates the neuroprotection conferred by social housing and increases infarct size to

the same size observed in socially isolated animals (51). As circulating IL-6 concentrations remain among the most widely used early predictors of patients' stroke severity and outcome, further insight into the role of central IL-6 signaling is essential for the development of therapeutic treatments involving modulation of inflammatory processes in stroke and cardiac arrest patients.

Proinflammatory cytokines such as interleukin 1 beta (IL-1 β), tumor necrosis factor alpha (TNF- α), and IL-6 are critical regulators of cerebral ischemia outcome. These cytokines are produced by microglia, which act the brain's principal local inflammatory response to brain trauma and are thus activated within minutes of the onset of cerebral ischemia (reviewed in 64). Although microglial activation (microgliosis) is a key process to the removal of dead cells and regeneration following brain injury, elevated and prolonged microgliosis tips the balance toward unchecked neuroinflammation which contributes to further neurodegeneration and inhibits recovery. While cerebral ischemia increases brain microglial expression, socially housed animals exhibit modest levels of microgliosis relative to social isolation (49,51,53). Importantly, the reduction of microgliosis is accompanied by reduced neuronal damage (49,53). These data provide compelling evidence for a role for neuroinflammation as a mechanism by which social interaction influences health.

Stress/Glucocorticoids

A substantial research effort has focused on the role of stress responses as a mediating variable in the relationship between social interaction and disease. Although basal glucocorticoid concentrations are typically similar between socially housed and isolated rodents (36,65–66), stress reactivity is attenuated in socially housed animals (39, 59, 67; but see Sanchez et al., 1998). Acute stress responses may be adaptive in many circumstances, but chronic stress is well-documented as being detrimental to health. In fact, chronic stress (such as chronic social isolation) leads to altered immune function (68–69), hypertension, myopathy (70–71), and a range of psychological disorders (72–73) to a similar extent in humans and animals. Further, social stress, such as social hierarchy disruption and intruder aggression results in glucocorticoid insensitivity and tips the balance toward a pro-inflammatory state in mice, (74) leaving the organism more susceptible to disease.

One approach to studying the deleterious effects of stress is to identify the psychosocial factors that increase an individual's susceptibility to both psychological and physical stressors. The buffering effect of affiliative social interaction against stress represents one potential mechanism of social influences on health. For example, acute restraint elevates circulating cortisol concentrations and prolongs wound healing in socially isolated Siberian hamsters (*P. sungorus*), however, pair-housing eliminates the stress-induced activation of the HPA axis and ameliorates the effect of stress on wound healing (58–59). In fact, restraint stress has no impact on wound healing latency among pair housed hamsters. Moreover, the effect of restraint stress on wound healing in socially isolated hamsters is likely mediated by endogenous cortisol secretion, because adrenalectomized hamsters heal more rapidly (59). In addition, social disruption (an experimental model in which established social hierarchies are disrupted via introduction of an aggressive intruder male) substantially elevates circulating glucocorticoid concentrations and increases susceptibility to viral infection (75) and a variety of inflammatory diseases including pulmonary inflammation (76), asthma (77) and influenza (78). Taken together, the consequences of over-stimulation of the HPA axis and hypersecretion of glucocorticoids may be ameliorated by stable and affiliative social interactions.

Oxytocin

The health-promoting effects of social interaction are marked by substantial changes in neuroimmune and neuroendocrine markers. To date, a specific underlying mechanism for these effects remains unclear, however converging evidence from a rapidly growing collection of studies implicates a mediating role for OT. OT is produced in high concentrations in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus, which in turn project to the posterior pituitary, where OT is released to its central and peripheral targets (79). The biological activity of OT is mediated by the oxytocin receptor (OTR) and to a lesser extent, three vasopressin receptors. The OTR, a G protein-coupled receptor, is abundantly present in several regions, both in the brain and periphery; however, several structures (particularly nuclei of the hypothalamus and amygdala) are particularly important for the onset and maintenance of the effects of OT on social behavior. Numerous studies have implicated both causal and regulatory roles for OT in the context of animal social behavior. Indeed, central release of OT regulates a wide range of social behaviors, including pair-bonding, mother-infant bonding, social recognition, and aggression (80–82). Central infusion of OT facilitates the onset of social behaviors (83–85), while an OT receptor antagonist (OTA) nearly completely eliminates them (86). OT also suppresses the hypothalamic-pituitary-adrenal (HPA) axis in several species (reviewed in 68), which further facilitates aspects of social behavior such as social recognition and formation of pair-bonds (reviewed in 87).

A substantial gap in knowledge about the precise physiological mechanisms of the health-promoting effects of social interactions has begun to close as a result of the increasing use of animal models for a variety of disease/injury states. In addition to the ability to precisely control for social conditions, the use of animal models allows for direct manipulation of the endogenous physiological signals (i.e. OT) believed to be responsible for social influences on disease. Pharmacological manipulations of central OT signaling have recently identified that the positive impact of social housing on health outcomes can be eliminated by blocking endogenous OT receptors. Treatment with an oxytocin receptor antagonist (OTA) prevents the ability of social interaction to reduce cerebral infarct size and inflammation as well as to increase anti-oxidant defenses following an ischemic event. Moreover, central administration of OT to socially isolated rodents mimics the beneficial effects of social housing on cerebral ischemia pathophysiology, thus establishing a mechanistic link for OT as a mediating signal by which social interactions confer health-promoting effects (88). Pair-housing also facilitates wound healing in hamsters, an effect that requires central OT signaling (59). Indeed, treatment of pair-housed hamsters with an OTA eliminated the protection of social housing, increased wound size and delayed healing. However, the benefits of pair-housing were recapitulated in socially isolated hamsters by central treatment with an OT agonist, resulting in similar wound size and healing time as in pair-housed hamsters (59). In addition, OT is involved in pain modulation, and has been shown to have potent anti-nociceptive effects (89). Indeed, reduced allodynia (pain in response to a stimulus that does not typically evoke pain) in pair-housed mice is also mediated by central OT signaling (Norman et al., 2010). A critical finding in these studies is that social facilitation of pain and healing is blocked by central OTA, indicating a receptor-dependent mechanism for this environment-physiology interaction.

The mechanisms through which OT influences disease progression and outcome appear to involve anti-inflammatory and antioxidant properties of OT. OT administration alleviates tissue damage in a variety of animal models of injury including renal (90) and hepatic (91) ischemia/reperfusion injury, as well as sepsis-induced multiple organ damage (92), skin injury (93) and colitis (94). The protective actions of OT in these models are primarily anti-inflammatory, resulting in decreased levels of TNF α and IL-6 (90–91) as well as decreased neutrophil infiltration to the site of injury (90–92,94). In addition, OT has recently been

shown to have antioxidant properties (95). Subcutaneous OT treatment increases peripheral antioxidant content and alleviates oxidative stress in a number of disease and injury models (90,92–94). Indeed, OT scavenges peroxynitrite, prevents oxidation of low-density lipoprotein and inhibits lipid peroxidation (95), thereby reducing the potential for tissue damage.

Conclusions

Taken together, these data indicate that the effects of social interaction on health outcome can be reproduced using animal models, and further that socially isolated and socially housed animals mount quantitatively and qualitatively different pathophysiological responses to injury. Moreover, social interaction modulates neuronal damage, inflammation, and corticosteroid secretion, three important determinants of disease progression and long-term outcome. Further, endogenous OT represents a neuroendocrine mediator ideally suited to coordinate environmental inputs (i.e. social or stressful interactions) with physiology (i.e. inflammation, corticosterone secretion, oxidative stress).

Chronic diseases are physically and mentally debilitating, expensive, and leave patients highly susceptible to the effects of stress and isolation. The existing data on the consistently positive effects of social interactions on disease outcome support a further need of a convergence of correlational research in humans and the mechanistic research in laboratory animals as a means of improving health and well-being. Additional animal research will be necessary to identify the cellular and molecular mechanisms by which physiological processes are altered by social interactions. For example, single nucleotide polymorphisms within the oxytocin receptor gene are implicated in social cognition, stress reactivity and various psychopathologies (96–97); however, whether these polymorphisms also contribute to individual variability in health outcomes remains unknown. Additionally, the use of gene knockout and knock-in animals remains an invaluable tool for identifying molecular signals that couple social behaviors to physiology. For example, CD38, a receptor that triggers lymphocyte proliferation and immune responses, was recently identified as a critical regulator of social behaviors through the use of CD38 knockout mice (98). Whether CD38 mediates social influences on health has not been examined. Ultimately, characterizing the physiological underpinnings of social influences on health will increase our understanding of the individual differences that contribute to the severity and outcome of disease and injury and will fill a gap in knowledge about the relationship between psychosocial state and the neurological and functional outcome of pathological states.

Acknowledgments

Funding support: Funding support for this work was provided by supported by grants from the American Heart Association (Established Investigator Award to A.C.D. and predoctoral fellowship to K.K.), National Institute of Neurological Disorders and Stroke Behavioral Core Grant P30 NS045758 (to A.C.D.), National Institute of Neurological Disorders and Stroke Grant RO1NS40267–05 (to A.C.D.), and National Heart, Lung, and Blood Institute Grant RO1HL080249–01 (to A.C.D.).

Abbreviations

CRP	C-reactive protein
CVD	cardiovascular disease
HPA	hypothalamic-pituitary-adrenal axis
IL-6	interleukin-6

OT	oxytocin
OTA	oxytocin receptor antagonist
PVN	paraventricular nucleus
SON	supraoptic nucleus
TNFα	tumor necrosis factor alpha
MCAO	middle cerebral artery occlusion
CA/CPR	cardiac arrest/cardiopulmonary resuscitation

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Table 1

Health effects of social housing

Species	Sex	Social Housing Condition	Model	Outcome	Reference
C57BL/6 mice	M	Paired with OVX F for 2 weeks	60-min MCAO	↓Cerebral infarct ↑Functional outcome ↓CRP	(50)
C57BL/6 mice	F	Paired with OVX F for 2 weeks	90-min MCAO	↓Cerebral infarct ↑Functional outcome	(50)
C57BL/6 mice	M	Paired with OVX F for 2 weeks	60-min MCAO	↓Infarct ↓Edema ↑Striatal IL-6 ↓Circulating IL-6	(51)
C57BL/6 mice	M	Paired with OVX F for 2 weeks	60-min MCAO	↓Cerebral infarct ↑functional outcome	(51)
C57BL/6 mice	M	Paired with OVX F for 2 weeks	SNI	↓Allodynia ↓Prefrontal cortex IL-1β ↓Depressive-like behavior	(54)
ApoE ^{-/-} mice (C57BL/6 background)	M	Housed in groups of 12 for 20 weeks	Atherosclerosis	↓Cholesterol ↓Triglycerides ↓Plaque area	(99)
<i>Microtus ochrogaster</i>	F	Paired with same-sex sibling for 4 weeks	Autonomic regulation of the heart	↓Heart rate ↑Heart rate variability	(41)
C3H/e mice	M	Housed in groups of 5 for 2 weeks	CA/CPR	↓Hippocampal cell death ↓Hippocampal microglia ↓Hippocampal TNFα ↓Circulating corticosterone	(49)
<i>Peromyscus californicus</i>	M	Paired with OVX F for 2 weeks	Wound healing	↓Healing time	(58)
<i>Peromyscus eremicus</i>	M	Paired with OVX F for 2 weeks	Wound healing	↓Healing time	(58)
Watanabe Heritable Hyperlipidemic rabbit	M	Paired with same-sex conspecific 4 hours a day for 4 months	Atherosclerosis	↓Atherosclerotic lesions of aorta	(100)

Outcomes listed relative to social isolation. Abbreviations: OVX F (ovariectomized female); MCAO (middle cerebral artery occlusion); SNI (spared nerve injury); CA/CPR (cardiac arrest/cardiopulmonary resuscitation); CRP (C-reactive protein); IL-6 (interleukin-6); IL-1β (interleukin-1 beta); TNFα (tumor necrosis factor alpha).

Table 2

Health effects of exogenous oxytocin treatment

Species	Sex	Dose and Administration	Disease/Injury Model	Outcome	Reference
Sprague-Dawley rats	F	500 µg/kg i.p.	Hepatic ischemia/reperfusion	↓Serum TNFα ↓Hepatic oxidative stress ↓Hepatic neutrophil infiltration ↓Hepatic damage	(91)
Sprague-Dawley rats	F	1 mg/kg s.c.	Sepsis-induced colonic, hepatic and uterine damage	↓Oxidative stress ↓Hepatic neutrophil infiltration ↓Serum TNFα	(92)
Wistar rats	M	1 mg/kg i.p.	Renal ischemia/reperfusion	↓Serum TNFα ↓Renal oxidative stress ↓Renal neutrophil infiltration ↓Renal interstitial hemorrhage	(90)
Sprague-Dawley rats	F	500 µg/kg s.c.	Colitis	↓Colonic damage ↓Serum TNFα ↓Colonic oxidative stress ↓Colonic neutrophil infiltration	(94)
Sprague-Dawley rats	--	5 µg/kg s.c.	Thermal injury	↓Dermal structure damage ↓Serum TNFα and IL-6 ↓Gastric oxidative stress ↓Gastric neutrophil infiltration	(93)
Siberian hamsters	F	20 mg/kg i.p.	Wound healing	↓Wound size ↓Circulating corticosterone	(59)
ApoE ^{-/-} mice (C57BL/6 background)	M	1 µg/kg/hr chronic s.c. infusion for 6 wks	Atherosclerosis	↓IL-6 secretion from adipose tissue ↓Lesion in thoracic aorta	(101)
C57BL/6 mice	M	1 µg i.c.v. for 10 days	SNI	↓Prefrontal cortex IL-1β ↓Depressive-like behavior	(54)

Outcomes listed relative to vehicle treatment. Abbreviations: i.p. (intraperitoneal); s.c. (subcutaneous); i.c.v. (intracerebroventricular); TNFα (tumor necrosis factor alpha); IL-6 (interleukin-6); IL-1β (interleukin-1 beta).