

# Social buffering: relief from stress and anxiety

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Communication is essential to members of a society not only for the expression of personal information, but also for the protection from environmental threats. Highly social mammals have a distinct characteristic: when conspecific animals are together, they show a better recovery from experiences of distress. This phenomenon, termed ‘social buffering’, has been found in rodents, birds, non-human primates and also in humans. This paper reviews classical findings on social buffering and focuses, in particular, on social buffering effects in relation to neuroendocrine stress responses. The social cues that transmit social buffering signals, the neural mechanisms of social buffering and a partner’s efficacy with respect to social buffering are also detailed. Social contact appears to have a very positive influence on the psychological and the physiological aspects of social animals, including human beings. Research leading towards further understanding of the mechanisms of social buffering could provide alternative medical treatments based on the natural, individual characteristics of social animals, which could improve the quality of life.

**Keywords:** social buffering; stress responses; social affiliation; glucocorticoids; oxytocin

## 1. INTRODUCTION

Social animals live in groups and communicate with each other in order to cooperate and manage the group in such a way that is beneficial to each individual member. To date, most empirical studies of social influences on stress have focused on the negative, stress-inducing aspects of social interaction (Levine 2001; Buwalda *et al.* 2005). Social interaction and communication are essential not only for cooperation within a group, but also for protection from environmental threats; this is one of the most beneficial aspects of establishing a society. For example, social mammals communicate with other group members to inform them of danger using vocal (Seyfarth & Cheney 2003), visual (Liddell *et al.* 2005) and pheromonal cues (Regnier & Law 1968; Rottman & Snowdon 1972; Wheeler 1976; Kikusui *et al.* 2001). It is conceivable that social subjects feel safe when they are with other colony members, because companionship provides protection for the subject from environmental threats. Therefore, solitude itself can be a stressor to social mammals (Hatch *et al.* 1965; Valzelli 1973; Clancy & McBride 1975; Noble *et al.* 1976), and they may show a high stress response when socially isolated.

Highly social mammals have a distinct characteristic: when conspecific animals are together, they show a better recovery from aversive experiences. This phenomenon, termed ‘social buffering’, has been found in rats (Davitz & Mason 1955), guinea pigs (Hennessy *et al.* 2000), non-human primates (Coe *et al.* 1978; Levine *et al.* 1978; Mendoza *et al.* 1978)

and humans (Thorsteinsson *et al.* 1998). Social species can also display an ‘isolation syndrome’, in which isolated animals show high levels of stress responses to a variety of stimuli, including endocrine, behavioural and autonomic stimuli (Hatch *et al.* 1965; Valzelli 1973; Clancy & McBride 1975; Noble *et al.* 1976), when they are housed individually over a long period. In humans, social isolation has been related to a risk of physiological and mental pathogenesis (Rabkin & Struening 1976; West *et al.* 1986); on the other hand, social support can have a positive influence on human health (Cobb 1976; Ell 1996). Therefore, understanding the mechanisms of social buffering could certainly be beneficial for human health as well as animal welfare. Several types of studies have been conducted using social mammals as models, and this paper will discuss mechanisms of social buffering that allow animals to find relief from stressful experiences.

## 2. ORIGINAL FINDINGS OF RESEARCH INTO SOCIAL BUFFERING

### (a) *Behavioural findings*

Researchers have found that when conspecific animals are together in a semi-natural environment, there is a reduction in their stress level. For example, a cat’s fear of eating was reduced by observing a non-fearful cat eating (Measserman 1943) and a goat kid demonstrated a greater ability to tolerate a novel environment when it was accompanied by its mother (Liddell 1950). Davitz & Mason (1955) found that the fearful withdrawal of rats in an open field diminished when other rats accompanied them. In this experiment, fear-conditioned rats displayed decreased locomotor activity when they were exposed to the conditioned

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stimuli in a novel open field, but the presence of another non-fearful rat increased their locomotor activity, and the fear-conditioned rats showed higher affiliation behaviour towards other rats. It appears that when conspecific animals are together, fear is allayed, and fear reduction may contribute to the social attraction of individuals.

Researchers such as Ewer have found that social mammals are highly attracted to conspecifics, and that this affiliation behaviour is both powerful and persistent (Ewer 1968; Latané 1975; Taylor 1976, 1981). It has also been suggested that for rats, the opportunity to interact with an unrestrained conspecific animal is a powerful reinforcer. Latané (1969) demonstrated that social affiliation behaviour in rats increased with repeated encounters, supporting the hypothesis that social affiliation activates reward mechanisms in the brain. In addition, Taylor (1981) found that stressed rats were more highly attracted to other animals than were non-stressed rats, indicating that stressed animals sought to encounter conspecific animals on their own, potentially to ameliorate negative emotions (Davitz & Mason 1955) or to obtain positive neurochemical rewards (Nelson & Panksepp 1998). Human subjects are also more likely to affiliate when under stress (Zucker *et al.* 1968; Teichman 1974; Morris *et al.* 1976; Friedman 1981), and a shared stress experience can lead to an increased attraction between partners (Latané *et al.* 1966). Therefore, it is possible that a human affiliation behaviour also activates a neural reward system (Aron *et al.* 2005).

#### (b) *Endocrine findings*

The first reported evidence of social buffering in non-human primates was demonstrated with mother–infant bonding in squirrel monkeys (Coe *et al.* 1978; Mendoza *et al.* 1978; Wiener *et al.* 1987). In those studies, infant monkeys showed an increase in cortisol when separated from their mothers, but if infants were placed in a familiar social environment containing colony members, the plasma cortisol responses were lower after the separation from their mothers. This evidence suggests that a familiar environment, which includes companions, has an ameliorating effect on stress response in infant monkeys. When the researchers conducted different procedures in which adult monkeys were exposed to fear-conditioned stimuli or snakes, they found that multiple companions, rather than a single familiar partner, were effective in stress amelioration after the stress exposure (Coe *et al.* 1982; Stanton *et al.* 1985). Based on these findings, research into the effects of social buffering has focused on neuroendocrine responses to a variety of stress episodes and in a variety of social contexts; presently, the neural mechanisms of social buffering are the target of study.

### 3. SOCIAL BUFFERING/ENDOCRINE EFFECTS

#### (a) *Stress–endocrine response*

An organism's response to an aversive situation depends not only on the severity and type of stressor, but also on how past experiences and available coping options style its perception of the stressful event. Selye

is the most recognized name associated with stress response and coping style. He was the first to bring attention to the major role played by adrenocortical hormones in physiological responses to stress (Selye 1956). So far, the observed increase in adrenocortical hormones after stress episodes has been the most widely studied phenomenon and the most dependable index of endocrine response to stress. There is an increase in adrenocortical hormones during psychological challenges (Mason 1968) and as a response to deleterious physical stimuli. The most essential regulating system of adrenocortical hormone secretion is a stress–neuroendocrine axis, called the hypothalamic–pituitary–adrenal (HPA) axis. Three primary hormones are involved in the HPA axis endocrine regulation. One is the corticotrophin-releasing factor (CRF), which is synthesized in the paraventricular nucleus (PVN) of the hypothalamus (Vale *et al.* 1981), and released into a portal blood vessel. CRF acts on the pituitary and stimulates the adrenocorticotrophic hormone (ACTH); it is the major physiological regulator if the increased HPA activity occurs as a response to stress. This has been demonstrated with data showing that the administration of CRF antisera almost completely blocked the pituitary–adrenal responses to a variety of stressors (Rivier & Vale 1983). ACTH travels through the peripheral circulation and stimulates synthesis and secretion of corticosteroids at the adrenal cortex. While ACTH is the major modulator of corticosteroid release, adrenocortical output can be modulated by neuronal inputs that adjust responsiveness to ACTH. The end effects of glucocorticoids' action include energy mobilization (glycogenolysis) in the liver, suppression of innate immunity in immune organs, inhibition of bone and muscle growth, potentiation of sympathetic nervous system-mediated vasoconstriction, proteolysis and lipolysis, suppression of reproductive function along the HPA axis and behavioural depression (Lombardi *et al.* 1991; Christensen & Kessing 2001). The wide variety of these effects suggests that glucocorticoids act to restore homeostasis following disruption (Munck *et al.* 1984).

#### (b) *Social buffering on HPA axis*

Studies investigating the social buffering effects on stress–endocrine activity have focused on the HPA axis. As described above, the first evidence of social buffering in non-human primates was demonstrated in squirrel monkey mother–infant bonding (Coe *et al.* 1978; Mendoza *et al.* 1978; Wiener *et al.* 1987), and Levine later reviewed details of these findings (Levine *et al.* 1997; Levine 2000, 2001). One simple example of the above phenomenon was that mother monkeys who lived separately from a group showed an increase in cortisol after their infants were removed, but mothers who lived in groups did not (Mendoza *et al.* 1978). In the paradigm of mother–infant separation, the cortisol response was also observed in infant dyads. However, if the infant monkeys were accompanied by familiar group members in a familiar environment, the cortisol response to separation decreased significantly, indicating that a familiar environment including group members produced social buffering effects in infant monkeys (Levine 2000). Being accompanied by a

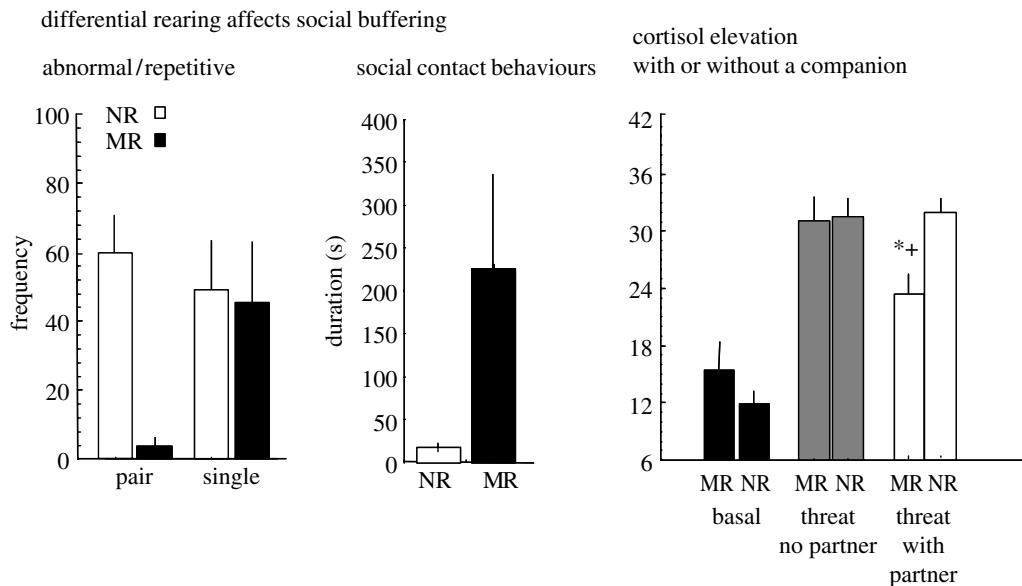


Figure 1. Behavioural and cortisol responses to separation stress of mother- or nursery-reared rhesus monkeys. Data represent behavioural and endocrine responses of nursery-reared (NR, open symbol and bars) and mother-reared monkeys (MR, closed symbol and bars) to a 30 min novel cage test with (pair) and without (single) a familiar social companion. (a) The mean ( $\pm$  s.e.m.) frequencies of abnormal/repetitive behaviour. (b) The mean ( $\pm$  s.e.m.) time engaged in social contact behaviour. The plasma levels of cortisol depicted in (c) represent samples collected within 5 min of capture (basal) or after 30 min in a novel cage with and without a social companion. Asterisk represents  $p < 0.05$  determined by Mann–Whitney  $U$  comparisons. For cortisol, asterisk represents cortisol differences ( $p < 0.05$ ) between single and paired conditions measured by paired  $t$ -test, whereas plus symbol represents differences ( $p < 0.05$ ) between NR and MR monkeys within condition measured by an independent  $t$ -test.

familiar group member has social buffering effects not only with regard to social separation stress, but also to natural threats. For example, exposing group-housed adult monkeys to a live snake, one of the most agitating stimulations for monkeys, induced avoidance behaviour, but did not produce an increase in cortisol response (Coe *et al.* 1982). Systematic aversive stimulation also increased cortisol levels in squirrel monkeys, and the presence of a familiar partner also decreased the neuroendocrine response to stimuli, as demonstrated by the classical fear-conditioning paradigm (Stanton *et al.* 1985). In this paradigm, the monkeys were first conditioned with the associations of cue stimuli (lighting) and aversive stimuli (shock). Thereafter, the monkeys were exposed to the cues and demonstrated an increase in cortisol levels. However, if a monkey was with a familiar partner, there was a lesser increase in cortisol production. These data indicate that the presence of social partners ameliorates the neuroendocrine response to various types of stressors. It is worth noting that the size of a social group also modulates the efficacy of social buffering. When the monkeys were exposed to a live snake, they exhibited an increase in cortisol levels, even when accompanied by a partner, suggesting that in this species, a certain amount of social stimuli from group members is required for social buffering. Gust *et al.* (1993, 1994, 1996) demonstrated social buffering in rhesus monkeys, in which existence of companion ameliorated separation or novelty induced cortisol levels. Contrary to the squirrel monkeys, pair housing was enough to cause a social buffering effect on neuroendocrine responses to novelty stress in rhesus monkeys, as demonstrated by the fact that mother-reared monkeys had a lower cortisol response to a novel environment when accompanied by a partner (Winslow *et al.* 2003).

Therefore, there might be differences between species with regard to the effects of group size on social buffering.

Winslow *et al.* (2003) demonstrated that the efficacy of neuroendocrine response with regard to social buffering in a novel environment is modulated by the conditions in which the subject animals were reared (figure 1). In their experiment, mother-reared or human nursery-reared monkeys were subjected to a novel environment with or without a cage mate. The monkeys reared by their mothers exhibited a reduction in cortisol response when a social partner was available, while nursery-reared monkeys did not. Moreover, social contact, such as allogrooming and intermale mounting, was drastically reduced in nursery-reared monkeys. These data suggest that nursery-reared monkeys have lower levels of social communication in a novel environment, which resulted in reduced efficacy with respect to social buffering involving cortisol responses.

Rodent models showed similar social buffering results in neuroendocrine responses to stress. If rats were exposed to a novel environment with partner rats, they showed a lower corticosterone response than solitary animals did, which were also exposed to the novel environment (Armario *et al.* 1983a,b). Studies on monogamous species such as the prairie vole and titi monkey demonstrated that these species showed an increase in corticosterone after the individuals were separated from their bonding partner in a novel environment; when pairs were reunited, corticosterone levels dropped (DeVries 2002). When the rats were exposed in a novel open field, their secretion not only of corticosterone, but also of prolactin, which is released from the pituitary under conditions of stress, decreased (Wilson 2000).

**(c) Social buffering on PVN**

Stress–endocrine responses are mainly mediated by PVN, which contains CRF neurons. The social buffering effects have been observed as neural activity in PVN, assessed by immediate early gene product c-Fos immunoreactivity (Kiyokawa *et al.* 2004c). In that experiment, rats were first fear-conditioned to a shock box, then re-exposed to the box with or without a partner. The rats re-exposed to the box showed an increase in freezing and a decrease in activity, as well as an increase in PVN c-Fos immunoreactivity; however, if the rats were accompanied by a partner, c-Fos immunoreactivity decreased in comparison with solitary animals that were also exposed to the box. Similar results were obtained from another study, in which sheep were introduced to a novel environment and researchers measured their mRNA expression level of *c-fos* and *zif268*, another immediate early gene, assessed in the PVN (da Costa *et al.* 2004). Interestingly, visual presentation of pictures of sheep faces was sufficient to induce social buffering in terms of behavioural, endocrine and autonomic responses to stress. These visual stimulations also ameliorated expression levels of *c-fos* and *zif268* mRNA in the PVN, indicating that social buffering effects were mediated at the level of PVN and, as a result, corticosterone decreased.

**4. CUES RESPONSIBLE FOR SOCIAL BUFFERING**

Cues that contain information leading to social buffering are released from partner animals and perceived by receivers. Social cues creating the effect of social buffering are varied among species and experimental contexts. The reason for this is that the tools used to inform animals of another animal's social or emotional state vary widely; a single species may use several cues to communicate social information to conspecific animals, depending on the circumstances. Therefore, an ethological viewpoint is important when trying to understand the cues responsible for social buffering.

**(a) Tactile cues**

In rats, tactile direct contact is an important cue for inducing social buffering. Latané (1969) demonstrated that social interaction between a free-moving dyad reduced the novelty-induced fear response, but this was not effective in a caged rat. In juvenile rats, the prolactin response to novelty stress was negatively related to the number of play bouts with a free-moving rat, and this ameliorating effect diminished if the partner was introduced in a cage (Wilson 2001). As described below, oxytocin may be a key mediator of social buffering; release of oxytocin was observed in animals that were subjected to non-noxious tactile stimulations, warm temperature and vibration, all of which are likely to activate somatosensory afferents caused by social contact and grooming (Uvnas-Moberg *et al.* 1993; Nelson & Panksepp 1998). However, studies have also reported that the amount of social interaction is not correlated with the HPA axis reduction in rats (Cirulli *et al.* 1996) and guinea pigs (Graves & Hennessy 2000; Hennessy *et al.* 1995b), implying that not only quantitative, but also qualitative

social interaction is important in the transmission of social buffering.

Social contact/behaviour is also important for transmitting social buffering in rhesus monkeys. As described above, Winslow *et al.* (2003) conducted an experiment in which mother- and peer-reared monkeys were subjected to a novel environment with or without cage mates. In nursery-reared monkeys, social contact, such as allogrooming and intermale mounting, was drastically reduced, accompanied with a lack of social buffering efficacy. These data suggest that because nursery-reared monkeys have less social contact in a novel environment, social buffering of cortisol reactivity is impaired. This impairment may have profound consequences for the impact of repeated stresses in the life history of these animals.

**(b) Olfactory cues**

Recently, studies have examined a comparative spectrum of effects induced by olfactory cues. Ågren *et al.* demonstrated that injecting oxytocin into a rat's cage mate induced reduction in ACTH and corticosterone, and prolonged withdrawal latency to heat stimuli in the non-treated rat (Ågren *et al.* 1997; Ågren & Lundeberg 2002). When olfactory cues were removed by nasal lesion in subject rats, this effect disappeared, indicating that social buffering is mediated by chemical cues. In rodents and other species, chemical communication is important for transmitting certain kinds of information, such as information about sex, age, dominant hierarchy, health, kin relationship and emotion. Exposing rats to a pheromone of alarm increases behavioural vigilance, stress-induced hyperthermia and Fos immunoreactivity in the PVN, suggesting that chemical cues can transmit emotional status to conspecific animals (Kikusui *et al.* 2001; Kiyokawa *et al.* 2004a,b, 2005b). Moreover, odours from the neck region have ameliorating effects on stress-induced tachycardia in rats, implying that an appeasing pheromone exists (figure 2; Kiyokawa *et al.* 2005a). In applied animal sciences, there is a commercially available appeasing pheromone, which may have an anti-stress property, for dogs, cats, pigs and horses (Guiraudie *et al.* 2003; Sheppard & Mills 2003). In pigs, this appeasing pheromone is found on the peripheral region of lactating nipples, and it attracts piglets to the nipples (Morrow-Tesch & McGlone 1990). When used within a group of unfamiliar piglets, it can reduce agonistic behaviour among them (McGlone *et al.* 1986). Pig appeasing pheromones can also have a positive effect on adult female pigs (Yonezawa *et al.* in preparation). Studies on humans have shown that maternal breast odour has an attractive property to infants, and it has been shown to elicit positive responses in babies (Porter & Winberg 1999). Therefore, chemical cues may modulate social buffering in some species, including human.

**(c) Vocal cues**

Some species use vocal communication to transmit their emotionality and familiarity. South American New World monkey marmosets exhibit a variety of vocal communication. They form heterosexual bonding units for cooperative infant care and, in this situation, they use a 'voice signature' for individual

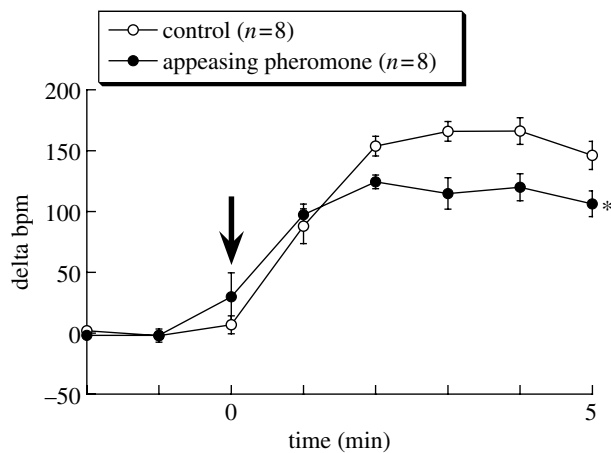


Figure 2. Odours released from the neck region of male rats decreased the heart rate response in the novel environment, implying that rats use odour cues for social buffering. Odour was collected from the anaesthetized rats, which were given regional electrical stimulation to the skin of neck.

identification (Sonwdon & Cleveland 1980; Jones *et al.* 1993). Rukstalis & French (2005) demonstrated that the separation of bonded partners increased urinary cortisol levels, and that hearing a bonding partner's voice, as compared to an unfamiliar marmoset voice, or to no auditory stimulation, attenuated cortisol levels. Therefore, in species that use voices, vocal buffering may be effective for the communication of emotions and attachment identification.

#### (d) Visual cues

When sheep were exposed to a novel pen, the presence of a peer from the same flock reduced corticosteroid secretion. In this species, visible cues are enough to induce social buffering effects. Da Costa *et al.* (2004) conducted an experiment in which socially isolated sheep were exposed to pictures of faces of familiar sheep, goats or to an artificially reversed triangle. They measured behavioural, autonomic, endocrine and neural responses to the stress of isolation. Sheep exposed to familiar sheep faces showed a decrease in these responses, as compared with other groups of sheep. Visible cues may contain enough information to transmit social buffering signals in sheep, because they use visual information to understand emotionality and familiarity in other sheep (Peirce *et al.* 2000; Kendrick *et al.* 2001; Broad *et al.* 2002). Humans also depend on visual information to communicate emotional status and familiarity (Morton & Johnson 1991; Morris *et al.* 1996). It is very possible that visual information transmits social buffering signals and stimulates its effects; recent imaging studies have indicated that pictures of the face of a loved one or of one's own children deactivate the amygdaloid nucleus, which controls fear-related responses (Bartels & Zeki 2000, 2004). Generally, it is a common practice to place pictures of one's family or a loved one on a desk or shelf, and it is possible that individuals may feel relieved when looking at the pictures after an experience involving stress; this offers some indication that visual information has a social buffering effect in humans.

Understanding what kinds of cues are important for social buffering in specific species might be related to

understanding how a particular species communicates emotional states and familiarity. If a species uses a number of sensory cues to communicate among themselves, each cue may contribute to the creation of social buffering effects, and when the recipient integrates such information, social buffering effects, therefore, appear. For example, human beings use many sensory cues for communication and, consequently, they need higher cognitive functions to integrate information about individual recognition, familiarity, kin relationship and emotional status. Thus, each type of sensory cue may contribute, in different degrees, to the creation of social buffering effects, but the actual presence of a partner in this communication constitutes the most effective sensory cue.

## 5. PARTNER'S EFFICACY IN SOCIAL BUFFERING

### (a) Familiarity of the partner

The presence of a conspecific animal is sometimes a stressor and sometimes a stress ameliorating stimulation. The outcome in this situation may depend on the context in which there is a dyad encounter. For example, if a male rat encounters another male rat in his territory, the presence of the other party becomes a stressor for both sides (Miczek 1974, 1979), but if a male rat is accompanied by another male in an anxious and novel situation, the existence of the other party may become a stress ameliorating stimulation. It is important to note that the familiarity of a partner is another factor which can influence what the presence of another party means to a subject. Monogamous male prairie voles show aggressive behaviour when they encounter unrelated subjects, even females (Williams *et al.* 1992; Winslow *et al.* 1993a,b). On the other hand, the presence of a bonding partner induces social buffering effects, such as a decline in corticosterone levels (DeVries 2002). Similar results have been obtained in monogamous species, such as the titi monkey (Hennessy *et al.* 1995a) and the Siberian hamster (Castro & Matt 1997a,b). It may be that efficacy with respect to social buffering depends on the degree of affiliation/attachment between subject and partner. Social attachment can be distinguished from social affiliation; when a social attachment is broken, animals show separation anxiety as well as activation in the HPA axis response, but this is not the case with social affiliation (DeVries 2002). As described previously, the presence of the mother in a squirrel monkey mother-infant dyad was enough to induce social buffering effects in infant monkeys separated from their group. Multiple familiar (not mother) adult monkeys were needed to create the same effect. This implies that a bonded partner is more effective in inducing social buffering (Coe *et al.* 1982; Stanton *et al.* 1985). Partner familiarity has also been observed to influence social buffering effects in rodents. In rats and guinea pigs, a familiar partner was more effective with respect to social buffering as far as behavioural and endocrine responses to stress were concerned (Terranova *et al.* 1999; Graves & Hennessy 2000; Hennessy *et al.* 2000, 2002); however, a number of controversial studies have reported that an unfamiliar partner is more effective (Armario *et al.* 1983a,b), or

that familiarity had no effect (Cirulli *et al.* 1996). Since the presence of a conspecific animal can induce aggression, dominant–subordinate relationships, sexual interaction, play behaviour, and so on, it is important to understand the kinds of subject involved, i.e. their sex, age, species, social history, and how familiar animals have been housed, as well as the kind of context the dyad is exposed to during the stress experience.

In guinea pigs, the presence of a mother reduces HPA activation during either pre- or post-weaning, not only in the period of infancy, but also in the periadolescent period (Graves & Hennessy 2000). A reduction in HPA activity was also observed when young guinea pigs were accompanied by another female guinea pig, but not by males (Graves & Hennessy 2000). In terms of persistence of the ability, it is also important to note that the biological mother was more effective than an unrelated female guinea pig (Hennessy *et al.* 2002), indicating that kin relationships also influence the efficacy of social buffering. The persistent ability of biological mothers to reduce HPA activity in their offspring has also been found in squirrel and titi monkeys (Hennessy *et al.* 1995a). When these species are observed in the wild, weaned infant monkeys continue to follow their mothers; therefore, in these species, a weak bond may continue to exist between mother and infant after weaning.

#### (b) *Emotional status of the partner*

Recent studies have demonstrated that emotional status is also important to the efficacy of social buffering (Kiyokawa *et al.* 2004c). We used the classical fear-conditioning paradigm; subject rats were conditioned by an association of contextual cues (exposure to a shock box) and aversive stimuli (foot-shocks). One day after the conditioning day, the subjects were re-exposed to the shock box with either a previously shocked partner that had also been fear-conditioned or a non-shocked partner. We examined behavioural, autonomic and c-Fos expression in the PVN in response to exposure to the shock box. As expected, being accompanied by a partner decreased the stress-related response, but if the subjects were re-exposed with a non-shocked partner, stress responses of behavioural, autonomic and Fos expression decreased even more, suggesting that the emotional status of a partner affects the efficacy of social buffering. Davitz & Mason (1955) demonstrated similar results in rats; fearful withdrawal in an open field diminished when rats were accompanied by another rat. In their experiments, fear-conditioned rats displayed less locomotor activity when they were exposed to the conditioned stimuli in a novel open field, but the presence of another non-fearful rat increased their locomotor activity, and fear-conditioned rats showed higher affiliation behaviour towards other rats. It is worth noting that if a subject was accompanied by a fearful rat which had been fear-conditioned in the same way, social buffering efficacy was diminished, suggesting that the emotional status of a partner is also important for efficacy in social buffering. As mentioned previously, tactile stimulation during social interaction seems to be the most important cue for transmitting social buffering in rats

(Latané 1969), hence we measured social interaction behaviour between the subject and the non-shocked or shocked partner. However, there was no obvious difference in terms of amicable social behaviour between a non-shocked and a shocked partner. There may be other cues that are responsible for transmitting a partner's emotional status.

## 6. NEURAL MECHANISMS OF SOCIAL BUFFERING

Several studies have focused on how information is processed in a receiver's central nervous system. As described above, tools for transmitting the effects of social buffering vary widely, meaning that various sensory systems receiving the information are involved in processing social buffering, and that sensory processing differs between species and experimental contexts. A number of studies suggest that social buffering has positive effects on health and stress responses, but little is known about the physiological and the neurochemical mechanisms through which positive social interactions suppress corticosteroids (Cohen 1988; Uchino *et al.* 1996; DeVries *et al.* 2003).

#### (a) *Oxytocin*

Neuropeptide oxytocin has been a candidate molecule for transmission of social buffering information (figure 3). Oxytocin plays a major neuroendocrine role, modulating diverse physiological functions, such as parturition and lactation in mammals (for a review, see Ludwig 1998; Russell & Leng 1998). During physiological and psychological stress responses, oxytocinergic neurons are activated, particularly in the paraventricular nucleus of the hypothalamus and secreted into the circulating blood (Ludwig 1998; Neumann 2002; Onaka 2004). Increase in oxytocin release from the hypothalamus inhibits HPA axis activation (Neumann *et al.* 2000; Neumann 2002; DeVries *et al.* 2003). Most natural observation about HPA axis suppression due to oxytocin has been conducted in lactating animals (Walker *et al.* 1995; Windle *et al.* 1997b; Neumann *et al.* 1998); nipple stimulation increases oxytocin levels peripherally and centrally, and it is accompanied by a decrease in cortisol levels (Chiodera *et al.* 1991; Amico *et al.* 1994). In humans, one study showed that breastfeeding after physical exercise attenuated an increase in cortisol as well as ACTH in the blood (Altemus *et al.* 1995). In rats, lactation blunted HPA activity in response to several stressors, including noise (Windle *et al.* 1997b), forced swim (Walker *et al.* 1995), exposure to cold (Adels *et al.* 1986) and lipopolysaccharide injection (Shanks *et al.* 1999). Oxytocin's ability to inhibit HPA axis can be mediated through three different levels. First, peripheral oxytocin acts on the adrenal gland to inhibit corticosteroid secretion. Legros *et al.* (1987, 1988) demonstrated that human males treated with exogenous oxytocin followed by synthetic ACTH showed a blunted response in cortisol secretion, suggesting that exogenous oxytocin inhibits corticosteroid synthesis in the adrenal gland. Second, Neumann *et al.* (1998) demonstrated that peripheral oxytocin inhibits ACHT release from the pituitary

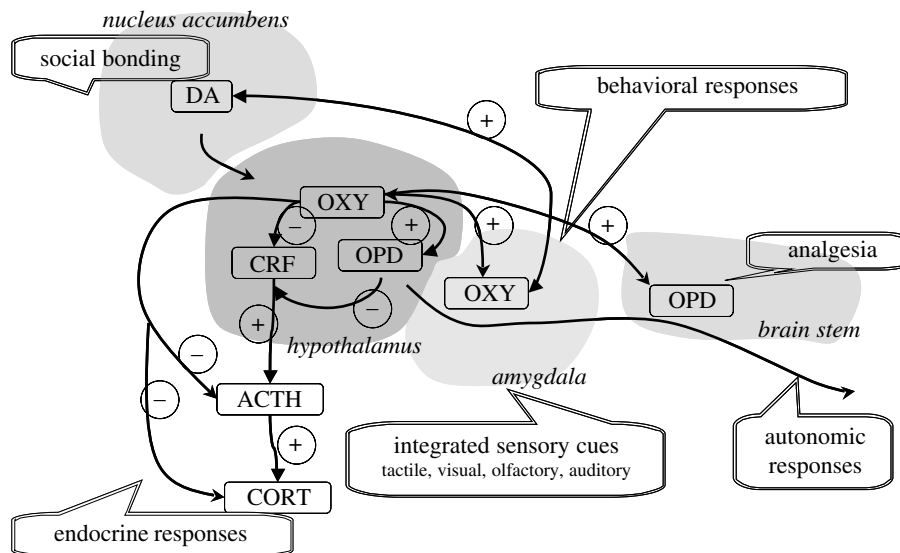


Figure 3. Schematic putative mechanisms of social buffering. Sensory cues, such as tactile, visual, olfactory and auditory ones, are transmitted from the senders to the receivers, which contains individual and emotional information. These information are integrated and transmitted to the amygdala. Oxytocin (OXY) release in the amygdala increases by social buffering cues, and they modulate behavioural responses to the stressors. Amygdaloid OXY has a positive effect on dopamine (DA) transmission in the nucleus accumbens, which is essential for social bonding. In addition, increase of OXY occurs in the hypothalamus, which is responsible for amelioration of stress neuroendocrine responses. Opioids (OPD) also have a modulating role in social buffering, reducing CRF activity in the PVN, and analgesia was found in socially stimulated animals.

gland. They injected exogenous CRF into lactating rats and measured ACTH responses, finding a reduction in ACTH response. Third, central oxytocin has inhibitory effects on the hypothalamic CRF activation. For example, intracerebroventricular injection of synthetic oxytocin decreased CRF mRNA responses to physical stress (Windle *et al.* 1997a, 2004; Carter 1998), and lactating female rats showed a similar decrease in CRF mRNA expression in response to stressors (da Costa *et al.* 2001). Studies have documented that in humans, the inhibitory property of exogenous oxytocin is mediated through the pituitary and adrenal glands (Legros *et al.* 1988; Chiodera *et al.* 1991), but recent articles have shown that intranasal administration of oxytocin, which passed directly into the brain (Born *et al.* 2002), suppressed cortisol response to psychological stress, as well as attenuated emotional functions after stress episodes (Heinrichs *et al.* 2003). Therefore, in humans, the inhibitory effect of oxytocin on HPA activity is also mediated in the central nervous system.

Oxytocin also causes a behavioural modification to stress response. In rodent models, it has been demonstrated that oxytocin has anxiolytic properties, as well as a significant role in the style of stress coping (Neumann 2002; Ebner *et al.* 2005), especially through modulating the central nucleus of the amygdala. Along with its stress-ameliorating effects, oxytocin seems to be involved in the social bond/affiliation behaviour of some mammalian species (Insel 1992, 1997; Winslow *et al.* 1993b; Young 2002; Young *et al.* 2002). Genetically manipulated mice lacking oxytocin exhibited the defect of social amnesia, whereas other reproductive behaviours were normal in both males and females (Ferguson *et al.* 2000, 2002; Winslow & Insel 2002, 2004). Oxytocin concentration in cerebrospinal fluid is positively correlated with social behaviour in rats (Haller *et al.* 1996). Moreover, recent findings suggest that central oxytocin is released in

response to physical contact (Uvnas-Moberg 1997) and induces excessive grooming when injected into the brain (Pedersen *et al.* 1988). In an experiment on rhesus monkeys, sociality was one of the main ways that information about social buffering was transmitted (Winslow *et al.* 2003). In that study, researchers assessed neuropeptide levels in cerebrospinal fluid and found that central oxytocin levels were lower in nursery-reared monkeys. Heinrichs *et al.* (2003) demonstrated that in humans, intranasal administration of oxytocin reduced anxiety levels, measured with the Trier Social Stress Test. Taken together, these results indicate that oxytocin attenuates not only the HPA axis response to stress, but also reduces negative emotions by increasing social affiliation behaviour. A recent study from Rilling *et al.* (2001) suggests that activation of the left dorsolateral portion of the prefrontal cortex may contribute to social buffering of stress-induced cortisol release in non-human primates. These findings are consistent with present models of the contributions of frontocortical structures to the processing of emotional stimuli by the amygdala (Davidson 2002).

#### (b) Opioids

The opioid system plays an essential role in the neural mechanisms of social attachment. Symptoms of opioid addiction may share similar properties with social attachment; both involve high levels of dependence, and withdrawal of stimuli induces agitation and anxiety behaviours (Panksepp *et al.* 1978, 1980). Several lines of investigation have been conducted, and it appears that opioids have ameliorating effects on separation-induced anxiety behaviour (Panksepp *et al.* 1978, 1980; Billington *et al.* 1990), and that social contact and interaction stimulate the release of opioids (Panksepp & Bishop 1981; Nelson & Panksepp 1998). Specifically, rat pups exhibited an increase in opioids when they were in

physical contact with their mothers (Carden & Hofer 1990a,b; for an opposing view, see Winslow & Insel 1991), and  $\beta$ -endorphin levels in monkeys increased after social grooming (Keverne *et al.* 1989). Recently, it was demonstrated that  $\mu$ -opioid receptor knockout mouse pups did not show attachment behaviour to their mothers, as assessed by ultrasonic vocalization (Moles *et al.* 2004). In adult mice, social contact induced analgesia, while this effect was blocked by administration of an opioid antagonist (D'Amato & Castellano 1989; D'Amato & Pavone 1996). Interestingly, the analgesia induced in mice by social contact was modulated by the familiarity of the partner; sib-pair mice showed higher analgesic symptoms than unrelated mice pairs (D'Amato 1997, 1998). These results indicate that greater social recognition is involved in analgesia induced by social contact, which is very similar to the transmission of social buffering effects. The neural opioid system has a strong rewarding effect, and this would explain why social animals are very attracted to conspecific animals (Ewer 1968; Latané 1975; Taylor 1976, 1981) and seek affiliation behaviour, resulting in the reduction of stress-related outputs.

### (c) *Interactions of oxytocin and opioids*

As described above, social affiliation behaviour has a rewarding effect; that is, social animals seek affiliation behaviour, and experience of this behaviour enhances the motivation for seeking it. These results indicate that social affiliation and attachment have a natural rewarding property; indeed, as Insel (1997) has claimed, 'Love is addiction'. Social bonding/attachment is the key factor in social buffering; when a social dyad establishes attachment, as in a mother–infant and pair bonding, they show an increase in HPA activity when separated. However, the partner's presence ameliorates stress neuroendocrine responses (DeVries 2002). Therefore, it is very possible that the neural mechanisms in social attachment are also involved in modulating social buffering. The neurobiology of social attachment has been reviewed extensively elsewhere, especially with regard to prairie voles (Insel *et al.* 1997; Young *et al.* 2001; Wang & Aragona 2004) and sheep (Kendrick *et al.* 1997; Kendrick 2004), hence only the main findings are mentioned here. Researchers have reported that establishing social attachment is involved in a neural reward system, such as dopamine and opioid systems (Nelson & Panksepp 1998; Young & Wang 2004). These two systems and the oxytocin system communicate with each other. Specifically, social stimulations such as mating and nipple suckling are key stimuli for establishing social attachments (Insel 1997; Insel *et al.* 1997; Carter 1998; Young *et al.* 2001; Kendrick 2004). These stimulations increase oxytocin release in mesocorticolimbic pathways; blocking the oxytocin neurotransmission abolished social attachment, indicating that an oxytocin pathway is indispensable for attachment (Insel *et al.* 1997; Kendrick 2004; Wang & Aragona 2004; Young & Wang 2004). Oxytocin neurotransmission amplified the mesolimbic dopamine system (Wang & Aragona 2004; Young & Wang 2004), suggesting that the reunion with a bonded partner after separation

increases dopamine transmission and reinforces social affiliation behaviours.

The release of opiate peptides is stimulated by oxytocin neurotransmission. Classical studies have demonstrated that chronic oxytocin treatment induced not only anti-stress effects, but also analgesia (Uvnas-Moberg *et al.* 1993); this analgesia effect was blocked by the opioid antagonist naloxone (Uvnas-Moberg 1997; Uvnas-Moberg *et al.* 1993), but not by an oxytocin antagonist, indicating that oxytocin increases endogenous opioid transmission. In both rats and humans, it was observed that lactating females showed analgesic symptoms in response to mechanical stimuli (Uvnas-Moberg 1996; Uvnas-Moberg & Eriksson 1996). Lim *et al.* (2004) also demonstrated that in prairie voles, local infusion of oxytocin increased preproenkephalin in the nucleus accumbens, suggesting that increase in oxytocin transmission activates neural rewarding systems and, as a result, established pair bonding. This increase of the endogenous opioid system via oxytocin may be the key mediator by which virgin females showed maternal 'sensitizing' behaviour with repeated exposure of neonate to the nipples. A lesion in the PVN, in which a large number of oxytocin neurons are present, results in diminished analgesia (Truesdell & Bodnar 1987), and descending oxytocin-containing fibres are projected to the spinal cord's dorsal horn (Robinson *et al.* 2002), an area important for processing nociceptive inputs. Other reports showed that effects of oxytocin on the HPA axis might be mediated via an opioid-dependent pathway, because pretreatment with an opioid antagonist abolished oxytocin effects on corticosteroid concentration (Douglas *et al.* 1998; Douglas & Russell 2001). Therefore, there may be complex communication between the oxytocin and the opioid systems, which is in turn involved in the neural mechanisms of social buffering.

## 7. CLINICAL ASPECTS

Studies on human subjects have demonstrated that social support significantly affects cortisol secretion (Kirschbaum *et al.* 1995) and cardiovascular and blood pressure responses to stress in laboratory settings (Gerin *et al.* 1992; Lepore *et al.* 1993; Uchino *et al.* 1996), and that it decreases the risk of cardiovascular diseases in clinical situations (Spitzer *et al.* 1992; Uchino *et al.* 1996; Gallo *et al.* 2000; Steptoe 2000; Uno *et al.* 2002). A positive social interaction/support has profound physical effects not only in human subjects, but also in laboratory animals. In many species, stress-induced hyperthermia and tachycardia are symptoms known to be associated with psychological stress. If the subject animals such as rats and sheep under stressful conditions are accompanied by a partner or social cues, these autonomic responses are ameliorated (da Costa *et al.* 2004; Kiyokawa *et al.* 2004c). In addition, social support can have positive effects on the risk of depression (Hays *et al.* 2001; Sayal *et al.* 2002), suicide (Rubenstein *et al.* 1998; Greening & Stoppelbein 2002), schizophrenia (Buchanan 1995; Erickson *et al.* 1998) and even stroke (Wyller *et al.* 1998).

Several clinical studies have shown that peri-ischaemic concentrations of corticosteroids can



augment brain injury (Koide *et al.* 1986; House *et al.* 1990; DeVries *et al.* 2001); a high concentration of corticosteroids may inhibit neuron ability to recover from damage. Positive social interaction can partially ameliorate cognitive and histological damage induced by experimental stroke in rodents (Hattori *et al.* 2000), and exogenous manipulations of corticosteroids levels have modulated social buffering effects on stroke symptoms (Sapolsky & Pulsinelli 1985). Decline in the HPA axis response to stress due to social support has other effects on physical functions. Wounds of socially supported patients healed faster than did wounds in non-supported patients (Rojas *et al.* 2002); this is mediated by adrenocortical hormones, and similar results have been obtained in experiments on animals (Detillion *et al.* 2004). In humans, the absolute number of T-cell subsets recovered more quickly with social support than when a solitary patient was exposed to a novel environment (Mohr & Genain 2004). It has been reported that diseases that respond to peripheral cortisol levels, such as cancer (Turner-Cobb *et al.* 2000; Spiegel & Sephton 2001; Miller *et al.* 2002), asthma (Buske-Kirschbaum *et al.* 2003) and infections (Cohen *et al.* 1997; Leserman *et al.* 2000; van Reenen *et al.* 2000) heal better in socially supported patients. Positive social relationships also increase oxytocin levels in humans (Heinrichs *et al.* 2003), and a high level of oxytocin induces long-term reduction in blood pressure and heart rate, as well as somatic growth (Uvnas-Moberg 1998). On the other hand, social stress and isolation are important factors in the aetiology of these diseases. Socially supported human subjects might consider the anticipated acute stressor as less threatening and more controllable than would an unsupported subject (Kirschbaum *et al.* 1995). Social support also affects foetuses. Morris *et al.* (1973) demonstrated that babies born from socially supported women had greater body weight than did babies from unsupported women. Social environments and relationships have opposite effects, mentally and physiologically: they sometimes cause negative symptoms, and are sometimes positive influences. It cannot be said that social union is always a good influence on human health, so an understanding of what kinds of relationships are positive or negative is critically important. Investigating the entire social buffering mechanisms, using animal models, could allow us to find a new approach to improving the quality of life.

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