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Social support modulates splenocyte glucocorticoid sensitivity in piglets exposed to social deprivation stress

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HIGHLIGHTS

- Maternal and littermate deprivation causes immune stress responses in neonatal pigs.
- Presence of a social partner attenuates the adverse consequences of social stress.
- The buffering effect was more pronounced in older relative to younger piglets.
- Social partners may enhance stress-coping abilities, which could promote health.

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ABSTRACT

There is growing evidence that positive social interactions can attenuate the effects of stressful life experiences. However, little is known about the benefits of social partners on stress responses in farm animals. Therefore, in this study we examined the effects of social support on the endocrine and immune stress responses to a single 4 h social deprivation in domestic piglets at 7, 21 or 35 days of age. The piglets were socially deprived of their mother and littermates. They were left alone (DA) or in the presence of a familiar (DF) or unfamiliar (DU) age-matched piglet. Non-socially deprived piglets served as a control. DA piglets displayed elevated plasma cortisol levels, higher lipopolysaccharide (LPS)-stimulated proliferation of splenocytes and increased TNF-α and IL-6 production in splenocyte cultures than the control piglets. There were no significant buffering effects of social partners on stress-induced plasma cortisol levels and splenocyte proliferation in response to LPS. However, the presence of an age-matched conspecific diminished the IL-6 production by splenocytes in younger, socially deprived piglets, and it reduced the TNF-α release in the older piglets. Compared to the controls, LPS-stimulated splenocytes from DA piglets were more resistant to the inhibitory effects of cortisol, which was demonstrated by a higher proliferative response and increased production of pro-inflammatory cytokines. The dose-dependent cortisol resistance was attenuated by the presence of a familiar or an unfamiliar conspecific at each of the three age categories. Indeed, in the present study, the familiarity level of the social partners did not seem to play a role in the alleviation of social stress-induced inflammatory activity and splenocyte cortisol resistance. In addition, the buffering effect of social support provided by an age-matched conspecific was more pronounced in older piglets. Conclusively, these findings suggest that social support is an important factor for enhancing piglets' abilities to cope with stressful challenges, and it may be a key approach needed to improve the health and welfare of farm animals.

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1. Introduction

Social relationships are a fundamental aspect of life that affects the functions of various biological systems and the ability to cope with challenging situations. While negative social interactions, such as the disruption of established hierarchies and experiences of social defeat or deprivation, can be sources of stress, social support or positive social behavior are known to attenuate the adverse physiological stress responses [1,2]. Thus, it is well established in social species that the presence of significant social partners reduces the activation of the hypothalamic–pituitary–adrenal (HPA) axis during times of stress [3–5]. Furthermore, studies in humans have demonstrated the protective effects of social support on immune functions and inflammatory processes and its positive implications for physical health and psychological well-being [6–8]. In contrast, information about the possible

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impacts of social support on animal health and immune responses is scarce. However, in animal husbandry, there is a growing interest in the assessment of social factors, such as the disruption of mother–infant interactions at weaning, so that we can extend our knowledge about the complex mechanisms of adaptation and can promote the health and welfare of farm animals.

Maternal separation and social isolation is a well-recognized model for studying psychosocial stress in pigs [9,10]. In previous studies from our group, we have demonstrated that a single social isolation (4 h) of piglets causes activation of the HPA axis, enhances behavioral arousal and increases neuronal activity assessed by a higher c-fos mRNA expression in the hypothalamus and amygdala [10]. Further, this isolation procedure induces immune alterations characterized by the redistribution of circulating lymphocytes and decreases in inflammatory cytokines in the plasma [11]. The changes in immune function after this short-term social stress were modulated by glucocorticoids (GC) and led to a state of cortisol resistance in peripheral blood immune cells [12].

In addition to circulating GC levels, the GC sensitivity of different immune cell targets from organisms exposed to stressors should also be considered when evaluating adaptive processes, potential imbalances, and increased health risks [13]. Although the rapid development of GC resistance may be an adaptive advantage for the organism to prepare the immune system for unpredictable danger or to heal cutaneous injuries [14,15], it may be maladaptive if the resistant individual has a predisposition to autoimmune or psychiatric disorders or is exposed to a bacterial endotoxin [16–19]. Thus, findings in mice suggest that the development of splenocyte GC resistance after social stress is a possible mechanism for the increased susceptibility to endotoxic shock [16].

The spleen is a highly organized lymphoid compartment that combines the innate and adaptive immune system, making it an important organ for immune homeostasis [20]. Spleen cells play a crucial role in initiating immune reactions to a variety of challenges, including pathogen exposure and stress [15,20]. Therefore, in the present study we used piglet splenocytes as a tool to investigate the acute modulation of immune cell GC sensitivity after social stress.

Social support is well known to be an effective factor in the amelioration of an individual's psychobiological reactivity to stressors and to reduce the risk for various diseases [4,5,21]. However, the effectiveness of social support seems to depend on the nature of the relationships between the individuals, e.g. the strength of social bonds, familiarity level and gender of social partners [5].

Based on these studies, we hypothesized that social support also can alter the immune functions of piglets for successful coping with psychosocial stress. To test this hypothesis, we examined the effects of social deprivation procedures on spleen cell immune functions (proliferation, cytokine production) and HPA activity (plasma cortisol release, splenic glucocorticosteroid receptor (GR)-binding) in piglets deprived of their mother and littermates without social support or with a familiar or unfamiliar conspecific at ages 7, 21 and 35 days. The sensitivity of spleen cells to GC inhibition was assessed by measuring in vitro cell proliferation and the production of cytokines (TNF-α, IL-6) in response to LPS with increasing cortisol concentrations. The responses of different socially deprived piglets were compared to non-socially deprived controls of the same age.

2. Materials and methods

All procedures, including use and treatment of animals, were in accordance with the German animal protection law and approved by the Committee on Animal Care and Use of the Agricultural Department of Mecklenburg-Vorpommern, Germany.

2.1. Animals and experimental procedure

A total of 108 piglets were taken from 27 German Landrace litters. The piglets were born and raised in the experimental pig unit of the Leibniz Institute for Farm Animal Biology (Dummerstorf, Germany). During the suckling period, sows and their piglets were housed in a loose farrowing pen (6 m^2) with plastic floor covered with sawdust and a water-heated lying area for the piglets at constant room temperature (28 ± 1 °C) and controlled lighting (12/12 h light/dark cycle, lights on at 0600 h), and with unrestricted access to food and water.

Four piglets from each litter were randomly allocated to four social treatments: (1) maternal and litter mate deprivation (piglets were separated alone, DA); (2) maternal and litter mate deprivation in the presence of a familiar conspecific (i.e., a piglet from the same litter, DF); (3) maternal and litter mate deprivation in the presence of an unfamiliar conspecific (i.e., an age-matched piglet from another litter without any previous contacts to the deprived piglet, DU); and (4) a control group without social deprivation (C) at 7, 21, or 35 days of age.

The allocation of male and female piglets within the groups was approximately equivalent (4 or 5 males and 4 or 5 females, $n = 9$ per treatment and age group). The piglets were separated from their mother and siblings in separate test rooms located in the same experimental station for one 4 h period in the morning (0700 and 1100 h). The piglets were placed either alone or with a familiar or unfamiliar age-matched conspecific in a wooden box (68 × 75 × 65 cm) with sawdust on the floor and adequate air passage. Within the box, the piglets were separated by a fine wire mesh. The socially deprived piglets were kept under the same air and temperature conditions as in the farrowing pen. The control piglets remained undisturbed in the farrowing pen during this time.

Before and after the social treatment, blood samples were taken from each piglet while the animals were in a supine position. The samples were collected by anterior vena cava puncture (the whole procedure lasted approximately 30 s), transferred to ice-cooled polypropylene tubes containing EDTA solution, placed on ice, and subsequently centrifuged at 2000 ×g for 15 min at 4 °C for plasma extraction. The plasma was then stored at −20 °C until cortisol analysis was performed. Immediately after the second blood sampling, the piglets were euthanized by an intravenous injection of T61® (embutramide/mebezonium iodide/tetracaine hydrochloride, Intervet, Unterschleißheim, Germany). The spleens were quickly removed and carefully dissected free of any extraneous tissue. Half of each spleen was aseptically placed in RPMI-1640 culture medium on ice until processing for immunological measurements. The other half was frozen in liquid nitrogen and stored at −80 °C for subsequent GR binding assay.

2.2. Analyses of cortisol and GR binding

Plasma cortisol concentrations were analyzed in duplicate using a commercially available ^{125}I-RIA kit (DSL Inc., Sinsheim, Germany) according to the manufacturer's guidelines. The cross-reactivity of the cortisol antibody was 33.3% for prednisolone and 9.3% for corticosterone, and lower than 5% for any further competing plasma steroids. The assay was validated for use with porcine plasma. The test sensitivity was 8.1 nmol/l, and intra- and inter-assay coefficients of variation (CV) were 8.2% and 9.8%, respectively.

GR binding in pig spleens was performed as previously described in detail by Kanitz et al. [22]. Briefly, spleen tissue was homogenized in a buffer solution (10 mM Tris–HCl, 12.5 mM EDTA, 10 mM sodium molybdate, 0.25 mM sucrose, 1 mM dithiothreitol) and centrifuged at 120,000 × g for 60 min at 4 °C to obtain cytosol (i.e., the supernatant fraction). Splenic GR binding was evaluated in saturation experiments using ^{3}H–dexamethasone (specific activity 70 Ci/mmol; Biotrend, Köln, Germany) over a concentration range of 0.2 to 24 nM. The bound ^{3}H–dexamethasone was separated from unbound steroid by precipitation with dextran-coated charcoal, and the receptor–^{3}H–steroid complexes were counted in a spectral liquid scintillation counter (LKB Wallac, Turku, Finland). Available GR was determined from the amount of total ^{3}H–dexamethasone binding that was displaced by the selective GR agonist RU 28362 (kindly donated by Roussel Uclaf, Romainville, France). Protein concentrations for each sample were determined by

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