

REVIEW ARTICLE

Social defeat models in animal science: What we have learned from rodent models

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ABSTRACT

Studies on stress and its impacts on animals are very important in many fields of science, including animal science, because various stresses influence animal production and animal welfare. In particular, the social stresses within animal groups have profound impact on animals, with the potential to induce abnormal behaviors and health problems. In humans, social stress induces several health problems, including psychiatric disorders. In animal stress models, social defeat models are well characterized and used in various research fields, particularly in studies concerning mental disorders. Recently, we have focused on behavior, nutrition and metabolism in rodent models of social defeat to elucidate how social stresses affect animals. In this review, recent significant progress in studies related to animal social defeat models are described. In the field of animal science, these stress models may contribute to advances in the development of functional foods and in the management of animal welfare.

Key words: depression, feed, metabolome, social defeat.

INTRODUCTION

Although animals and humans are continually affected by environmental stresses, such as heat, infection and aggression, they generally maintain a homeostatic balance via their endogenous strength, namely, resilience (Selye 1956). Unfortunately, strong and chronic stresses have marked effects on animal bodies and can induce various disorders. Abnormal behaviors are often observed under conditions of severe stress. In humans, several mental disorders are induced by stress, and major depression is a particularly common disease with a lifetime prevalence of 2%–20% worldwide (Weissman *et al.* 1996). Furthermore, stress management in animals, such as livestock, experimental animals and zoo animals, has recently become a more important issue, compared with over the past few decades, because of the increased worldwide focus on animal welfare (Grandin & Shivley 2015). Therefore, the various aspects of studies on animal stresses warrant investigation.

Social conflicts frequently occur in animal and human societies, and unavoidable stresses can worsen the quality of life in both animals and humans. In our research group, rat and mouse models of

social defeat have been developed and characterized in order to elucidate the mechanisms of psychiatric disorders such as depression. Moreover, rodent models of social defeat are applicable to group-housed animals on farms and in zoos, because social interactions among conspecific animals often induce serious stress, particularly in inferior animals. Therefore, the rodent models of social defeat can potentially provide significant and basic information for understanding several of the physiological and behavioral abnormalities induced by social stress between individuals.

Various animal models of depression were developed and widely used in depression studies (Nestler & Hyman 2010) (Table 1). Forced swimming and tail suspension tests, for example, are popular for screening antidepressants; however, there are serious concerns regarding the predictive validity of such acute stress models (Cryan & Holmes 2005). Acute administration of antidepressants can cure the 'depressive behavior' in these models, although only chronic

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Table 1 Representative depression models of rodents

Model	Stress type	Reference
Forced swim	Acute, physical, emotional	Porsolt <i>et al.</i> (1977)
Tail suspension	Acute, physical, emotional	Steru <i>et al.</i> (1985)
Mild stress	Chronic, physical, emotional	Willner (2005)
Maternal deprivation	Chronic, emotional	Schmidt <i>et al.</i> (2002)
Social defeat	Chronic, physical, emotional	Golden <i>et al.</i> (2011)
Subchronic social defeat	Chronic, physical, emotional	Goto <i>et al.</i> (2014)
Witness stress	Chronic, emotional	Sial <i>et al.</i> (2016)
LPS injection	Acute, chemical	Shen <i>et al.</i> (1999)

LPS, lipopolysaccharide

administration of antidepressants can alleviate the depressive symptoms in human patients. Among the depression models, the chronic unpredictable mild stress model (Willner 2005) and the chronic social defeat stress (CSDS) model (Miczek 1979) are more reasonable for depression studies compared to other acute stress models from the points of view of several validities (Cryan & Holmes 2005; Nestler & Hyman 2010). In particular, the mouse models of CSDS, which have been comprehensively studied using omics techniques, have produced significant knowledge about depression (Krishnan *et al.* 2007). Our research group has focused on deficits of behavior, nutrition and metabolism in CSDS models, and in this review recent progress in the use of CSDS models is described.

ANIMAL SOCIAL DEFEAT MODELS

Animals subjected to CSDS are good models for gaining an understanding of psychiatric disorders and abnormal behaviors in animals. Previously, rat (Miczek 1979), mouse (Krishnan *et al.* 2007) and hamster (Potegal *et al.* 1993) models of CSDS have been reported and extensively studied. Furthermore, pig (Ruis *et al.* 2001), zebra fish (Oliveira *et al.* 2016), *Drosophila* (Penn *et al.* 2010) and cricket (Rillich & Stevenson 2014) models of defeat have been developed and characterized. Figure 1 shows a

popular paradigm for production of mouse models of social defeat, using ICR mice as the resident and C57Bl/6J (B6) mice as the intruder (Golden *et al.* 2011; Goto & Toyoda 2015a). Aggressive ICR mice, which are screened before conducting the paradigm, are housed for a few days in a compartment of the home cage divided by a transparent acrylic board, which contains small holes that allow the circulation of odors, pheromones and vocalizations. Thereafter, a B6 mouse is introduced into the territory of an ICR mouse and the ICR mouse typically attacks the B6 mouse, which is characterized by chasing, grooming, and biting (physical stress). After a short duration of aggression, the B6 is moved to a neighbor compartment of the ICR and kept for the remainder of the day (psychological stress). The following day, the B6 mouse is subjected to another ICR mouse in the same manner. In the normal protocol, B6 mice are subjected to 10 daily sessions of physical stress and psychological stress, as described above, and these B6 mice become CSDS models that display various depressive-like features.

Although different versions of the paradigm for developing CSDS models are used for various purposes, it is generally not possible to prevent injuries to B6 subordinates from physical contact. Therefore, our protocol for the paradigm was modified and the duration of physical contact was reduced from 5 min to 30 s each day to minimize the severe injuries

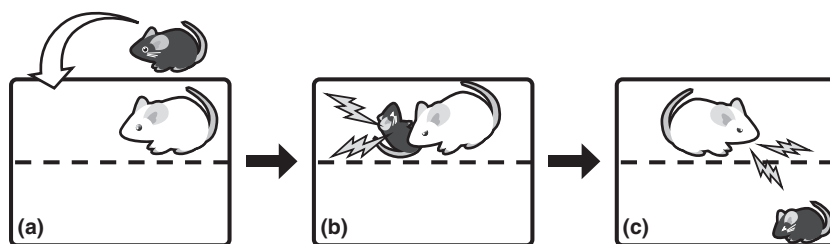


Figure 1 Development of a mouse model of social defeat. An ICR mouse is housed in a compartment separated by a transparent acrylic divider containing many holes (a). After a few days of habituation, a C57BL/6J (B6) mouse is introduced into this compartment, and normally the ICR mouse will severely attack the B6 mouse (b). After several minutes of this social conflict, the B6 mouse is moved to an adjacent compartment for the remainder of the day (c). The following day, the B6 mouse is subjected to social conflict with another ICR mouse. This sequence of physical and psychological stress is repeated for 10 days to induce depressive symptoms in the B6 mouse.

derived from biting by ICR mice (Goto & Toyoda 2015a). Our social defeat paradigm that involves less physical stress is considered to be appropriate for developing mouse models of human depression, because psychosocial and emotional stresses mainly impact human mood and precipitate mental disorders. Actually, our chronic social defeat model of mice showed several depressive symptoms as described below. Recently, a mouse model of defeat has been developed in which the focal mouse is made to witness stress (Sial *et al.* 2016). In this paradigm, only mental stress is induced by exposing a B6 mouse to conflict between ICR and B6 mice in an adjacent room. In this paradigm, therefore, the subordinate mouse does not suffer physical stress or wounding. As in the conventional mouse models of social defeat, various depressive symptoms, such as weight loss, decreased social behavior and anxiety, develop in mice that witness stress (Sial *et al.* 2016). Because chronic but not acute fluoxetine administration is effective in alleviating the depressive symptoms in model mice, the mice that witness stress satisfy the prediction validity of a depression model. Moreover, it has been reported that a BALB/c mouse model of social defeat shows greater vulnerability to stress than does the B6 mouse model (Savignac *et al.* 2011).

Normally, different strains of rodents are used as resident and intruder for the production of models of social defeat. Previously, we attempted to develop a CSDS model using Wistar rats as both resident and intruder; however, it was difficult to induce constant aggressive behaviors in resident Wistar rats. Therefore, we maintained an aggressive colony of Wistar rats as the residents in our laboratory and produced a Wistar rat model of chronic social defeat (Iio *et al.* 2011). For the CSDS paradigm in both mice and rats, the aggressive behaviors of residents are considered to be critical to achieve defeat model reproducibly. Since it has previously been described that aggressive ICR mice constantly attack B6 mice in less than 50% of encounters (Golden *et al.* 2011), it is important to conduct selection of aggressive residents before performing the CSDS paradigm, in order to produce a successful CSDS model. Recently, variations of the social defeat model, including a juvenile model and a female model have been reported (Iñiguez *et al.* 2014; Solomon 2017), and analysis of these models will enable us to gain a better understanding of stress-induced abnormal behaviors and psychiatric disorders such as depression.

BEHAVIORAL ANALYSIS

Mouse and rat models of social defeat have been widely characterized by various experimental techniques. In this section, the behavioral features of the

models, particularly those that are important in animal science, are described.

Eating behavior

Some eating disorders, including anorexia and hyperphagia, are frequently observed in depression (American Psychiatric Association 2013), and these symptoms are also observed in depression models. In the Wistar rat model of social defeat developed in our laboratory, the food intake and body weight gain of this rat model were suppressed compared to control rats (Iio *et al.* 2011, 2012a). These results are consistent with those obtained for another rat model of defeat (Rygula *et al.* 2005). Therefore, we focused on analyzing the mechanisms whereby food intake is suppressed in the rat model of social defeat (Iio *et al.* 2012a, 2014).

Although decreases in blood glucose level and leptin gene expression in adipose tissue were observed in the model rats (Iio *et al.* 2014), the level of malonyl-coenzyme A (CoA), a feeding regulator in the hypothalamus, was elevated (Iio *et al.* 2012a). Normally, the level of malonyl-CoA in the hypothalamus is increased by leptin and blood glucose, which suppresses eating behaviors via altered hypothalamic expression of several neuropeptides related to eating behaviors (Lane *et al.* 2008). Considering the peripheral metabolism of the rat social defeat model, it was assumed that the level of hypothalamic malonyl-CoA would be decreased. However, despite the low levels of peripheral leptin and blood glucose in the defeat model, the level of hypothalamic malonyl-CoA was abnormally increased to induce anorexia (Iio *et al.* 2012a). Furthermore, signals downstream of hypothalamic leptin in the rat social defeat model appeared to be normal (Iio *et al.* 2014). Consequently, CSDS may perturb the regulation of hypothalamic malonyl-CoA. In addition, anorexia in depressive patients may be linked to hypothalamic malonyl-CoA. Hence, by targeting malonyl-CoA and its related enzymes in the hypothalamus, it may be possible to develop novel therapeutic drugs for anorexia.

Eating behaviors have also been investigated in the mouse model of chronic social defeat. Krishnan *et al.* (2007) reported that CSDS decreases food intake and body weight in B6 mice. In contrast, Goto *et al.* (2014) described that CSDS does not decrease food intake, but instead increases body weight gain following polydipsia-like features. Because body water content also increases in CSDS mice compared to control mice, increased body weight gain may be attributable to polydipsia (Goto *et al.* 2014). Differences in the food intake and body weight of CSDS mice are considered to be dependent on factors such as the experimental environment, breeder and feed,

although the details are unknown. The food intake and body weight of CSDS mice may be influenced by the strength of physical contact with resident ICR mice. Indeed, a previous report has described that 10 days of CSDS (10 min/day) does not change body weight, but that 10 days of CSDS during which the intruder suffers only one defeat daily increases body weight compared to control mice (Savignac *et al.* 2011). As mentioned above, in order to reduce physical stress, such as that resulting from injuries inflicted by ICR mice, the protocol of the subchronic and mild social defeat stress (sCSDS) model has a reduced contact time with ICR compared to the standard protocol (Golden *et al.* 2011); therefore, sCSDS animals may not experience the severe stress that decreases food intake and body weight (Goto *et al.* 2014). As increases in food consumption and body weight gain are observed in depressive patients (American Psychiatric Association 2013), sCSDS mice will be a good model of depression associated with such symptoms. However, there may not be a simple correlation between the intensity of physical stress and food consumption and body weight gain, because a previous report has described that witnessing stress can also decrease body weight (Sial *et al.* 2016). A detailed analysis of this issue should therefore be carried out in the future. Furthermore, social defeat models of livestock should be developed and intensively investigated, because there is little information about the effects of social defeat stress on feeding and growth. Neuropeptides related to eating behaviors are known to be linked to depression (Lutter & Nestler 2009), and analysis of feeding behavior and related neuropeptides in various stress models may provide important insights into eating disorders and deficient body weight control.

Depression-like behavior

It is difficult to evaluate depressive behaviors objectively in mice and rats. What is the behavior associated with the face validity of the depression model? The forced swimming test (FST) and tail suspension test (TST) have been used to evaluate depression-like behaviors (Porsolt *et al.* 1977; Steru *et al.* 1985). Drugs showing antidepressant effects have been widely screened using the FST and TST, because some antidepressants can shorten the immobile behavior in these tests. Unfortunately, acute administration of antidepressants can reduce the immobility time in FST and TST, which is not consistent with clinical situations (Cryan & Mombereau 2004). In general, antidepressants are effective for depressive patients in chronic administration, but not acute administration. Therefore, drug screening using the FST and TST is not based on predictive validity for depression. Moreover, the immobility time of the

FST was extended in CSDS rats (Iio *et al.* 2011), but the immobility time of the FST and TST was not changed in sCSDS mice (Goto *et al.* 2014). In the case of bipolar disorder model mice, it has been reported that the immobility time of the FST was unexpectedly reduced (Kasahara *et al.* 2016). Collectively, the depression-like symptoms of mice and rats cannot be completely reflected in evaluation tests of despair such as the FST and TST. Accordingly, social interaction tests have been used to evaluate depression-like behaviors in social defeat models (Fig. 2a) (Golden *et al.* 2011; Goto *et al.* 2014; Goto & Toyoda 2015a). As shown in Figure 2a, a B6 mouse was introduced into an open field arena with or without an ICR mouse in a wire mesh box. The duration for which the B6 mouse remains in the interaction and corner zones are measured. Since normal and healthy B6 mice are motivated to explore, the B6 mouse approaches the ICR mouse (Fig. 2b). However, a B6 mouse subjected to CSDS avoids the ICR mouse (Fig. 2c), although, interestingly, some populations of CSDS mice show stress resilience characteristics (Krishnan *et al.* 2007).

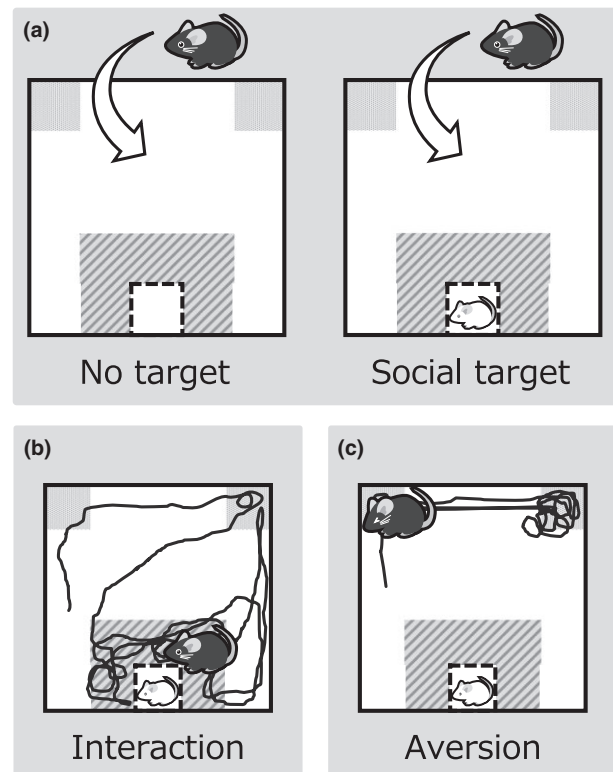


Figure 2 Social interaction test for evaluation of defeated mice. The social behavior of stressed and control B6 mice is monitored with or without ICR mice (a). Control and resilient mice engage in social interaction with ICR mice (b), whereas susceptible mice avoid ICR mice (c).

Various studies focusing on the difference between resilience and susceptibility have been carried out on the central nervous system (Krishnan *et al.* 2007; Golden *et al.* 2013; Bagot *et al.* 2015) and the immune system (Hodes *et al.* 2014), because the underlying mechanism of this stress vulnerability is likely to be linked to the pathology of depression. Recently, we revealed that resilience to social defeat stress is affected by diet (Goto *et al.* 2016a). Namely, mice fed a non-purified diet (MF) are more resilient than those fed a semi-purified diet (AIN-93G), although the mechanisms underlying this difference are not known. In future studies, the dietary substances that enhance stress resilience should be identified. Indeed, Yao *et al.* (2016) reported that the sulforaphane and glucoraphane contained in broccoli enhance resilience to social defeat stress. Therefore, it is assumed that various natural resources and foods, including plants and fruits, could increase stress resilience, and in the future, it will be fruitful to explore candidates for the medication of depression using social defeat models.

METABOLIC FEATURES OF RODENT MODELS OF SOCIAL DEFEAT

As described above, social defeat models have been analyzed using various biochemical and molecular biological methods, including comprehensive methods such as DNA microarrays (Krishnan *et al.* 2007). Recently, using metabolomics, we attempted to identify the metabolic pathways influenced by CSDS. Taurine levels in the liver and plasma of CSDS rats were shown to be higher than those in control rats (W. Iio *et al.*, unpublished data). Similarly, a clinical report has described that blood taurine concentrations in depressed patients are higher than those of controls (Altamura *et al.* 1995). Although details are unknown, depressive symptoms may be linked to blood and tissue taurine. Therefore, we focused on the effect of taurine on behavior and the central nervous system. Iio *et al.* (2012b) reported that taurine supplementation for 4 weeks had antidepressant-like effects because chronic taurine decreases the immobility time of the FST. Furthermore, Murakami and Furuse (2010) reported that chronic taurine administration produced antidepressant-like effects in mice. We therefore attempted to elucidate the hippocampal signal cascades that play a key role in depression in rats fed taurine (Iio *et al.* 2012b). Taurine supplementation for 2 weeks (45 mmol/kg diet) did not affect behavior in the FST; however, AKT, GSK3 β , ERK, and CREB were phosphorylated. Finally, CaMKII was phosphorylated for 4 weeks concomitant with taurine feeding, suggesting that phosphorylation of CaMKII is critical in

the antidepressant-like action of taurine (Iio *et al.* 2012b).

Metabolome studies were conducted in the plasma, liver and cecum digesta of sCSDS mice (Goto *et al.* 2015b; Aoki-Yoshida *et al.* 2016). Although no significant change was observed in the plasma metabolome of model mice, metabolites such as taurocyamine (GES), phosphorylcholine, alanyl-alanine, and 1-methylnicotinamide, in the liver were increased by sCSDS (Goto *et al.* 2015b). GES is a metabolite located downstream of taurine, and thus social defeat stress may have a general effect on taurine metabolism in the liver.

Social defeat stress causes brain dysfunction following inflammation in the peripheral tissues and central nervous system (McKim *et al.* 2016). Although the mechanisms whereby liver taurine and GES levels are increased by social defeat stress are unclear, the anti-inflammatory actions of taurine and its derivatives may be important for liver function under stressful conditions (Marcinkiewicz & Kontny 2014). Inflammation is, nevertheless, profoundly related to mental illness (Mechawar & Savitz 2016), and therefore future studies are needed to determine whether taurine supplementation would be effective in alleviating mental illness-related inflammation. Increases in cholic acid and decreases in 5-aminovaleric acid (5-AV) have been observed in the cecal contents of sCSDS mice (Aoki-Yoshida *et al.* 2016). Since cholic acid is an antagonist for *N*-methyl-D-aspartate (NMDA) and γ -aminobutyric acid (GABA) receptors (Schubring *et al.* 2012), increased cholic acid in the cecum digesta may affect the peripheral and central nervous systems. In addition, 5-AV modifies GABA neurons via various mechanisms (Nanavati & Silverman 1989; Fritsche *et al.* 1999), including inhibition of GABA uptake (Tasaka *et al.* 1989), inactivation of GABA aminotransferase (Nanavati & Silverman 1989), and acting as an agonist and antagonist for GABA β receptors. Furthermore, 5-AV suppresses convulsions in an epilepsy model (Dhaher *et al.* 2014). The decrease in 5-AV in the cecum of sCSDS mice may also affect neuronal activities and behaviors related to depression.

PERSPECTIVES FOR THE APPLICATION OF RODENT MODELS TO ANIMAL SCIENCE

Finally, I would like to describe the possible contributions that the study of rodent models of social defeat could make to animal science. The functional ingredients of animal products that prevent depression could be discovered by nutritional approaches using CSDS models. Furthermore, CSDS models will provide meaningful knowledge regarding animal welfare, particularly the management of social conflicts.

Discovery of foods and nutrients for the prevention of depression

It is believed that rodent models of social defeat are suitable for discovering foods and nutritional factors that could potentially play a preventative role in depression. Given that there are antidepressant-resistant patients, novel types of antidepressants such as ketamine, an NMDA receptor antagonist, are needed for clinical intervention (DeWilde *et al.* 2015). Recently, nutritional functionality has received attention with respect to the prevention of depression, because the intestinal environment and microbiota appear to be closely linked to various mental disorders (Lang *et al.* 2015; Stilling *et al.* 2016). Rodent models of social defeat will provide appropriate information regarding the type of nutrition suitable for preventing and treating depression. Unfortunately, it may be difficult to screen foods using social defeat models because some skills are needed for development and characterization of the defeat models. Simple and easy methods should therefore be developed for such screening using social defeat models.

Recently, we discovered that sCSDS mice delay nest-building behavior (Otabi *et al.* 2016). Mouse nesting behavior is a complex, innate and goal-directed behavior (Kinder 1927; Van de Weerd *et al.* 1997), and nest building requires attention related to particular areas of the frontal cortex and hippocampus (Kolb 1984; Carter *et al.* 2000; Deacon *et al.* 2002, 2003; Filali & Lalonde 2009). Because attention deficit is observed in depressive patients, nesting delay in sCSDS mice may represent one of the symptoms of depression. The deficiency in nest building behavior has been identified in various mouse mental illness models, including that of schizophrenia (Takao *et al.* 2013), whereas sCSDS mice can finally complete nests (Otabi *et al.* 2016). Similar symptoms have also been observed in a mouse model of Down's syndrome, and the symptoms of this delay in nest building were improved by antagonists of serotonin (5-HT) receptor 2A (Heller *et al.* 2014). Otabi *et al.* (2017) reported that acute social defeat stress also delays nest building and that this delay is partially rescued by a 5-HT_{2A} receptor antagonist. Therefore, a paradigm that consists of acute social defeat stress and an evaluation of nest quality will be a convenient tool for screening functional foods and reagents that could potentially contribute to the prevention and treatment of depression. Furthermore, in the future, automatic analysis systems for the evaluation of nest quality should be developed for efficient screening (Okayama *et al.* 2015; Goto *et al.* 2016b).

Application to animal welfare

Group-housed livestock are constantly affected by social stress and conflict. Because the social ranking

in group-housed pigs affects growth performance (Desire *et al.* 2015), it is very important for livestock farmers to successfully manage social conflict and hierarchy in livestock. Comprehensive studies on nutritional and metabolic features in rodent models of social defeat will promote the development of feed additives that could reduce the distress effects attributable to social stress and increase resilience in livestock. In this regard, a recent publication has described that feedstuffs for cattle affect not only meat quality but also animal welfare (Carrillo *et al.* 2016), and that blood cortisol levels strongly indicate that grass-fed animals may experience less stress than grain-fed individuals (Carrillo *et al.* 2016). Although the quality of feed has a profound effect on livestock welfare, it remains difficult to conduct comprehensive and reproducible studies on this issue using livestock. We have found that feed purity influences stress resilience in mice (Goto *et al.* 2016a, b); therefore, we believe that rodent models provide relevant information relating to feeding management under stressful conditions. Moreover, zoo animals are exposed to various stresses, and abnormal behaviors such as pacing are frequently observed (Koyama *et al.* 2012). In addition to environmental enrichment, efforts should be made to discover the feeding conditions that could suppress such abnormal behaviors in zoo animals.

Conclusion

Recent studies have revealed that observations on socially defeated rodents can potentially contribute not only to research on depression but also to various studies in animal science. This is because there probably exists a common mechanism for coping with stress in any social group of animals, including humans, experimental animals, livestock and zoo animals. Animal science researchers are expected to utilize and study the social defeat model from various aspects, which will promote a global understanding of the effects of social stress on animal nature.

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REFERENCES

- Altamura C, Maes M, Dai J, Meltzer HY. 1995. Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. *European Neuropsychopharmacology* **5**(Suppl), 71–75.
- American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*, 5th edn. American Psychiatric Association, Arlington, VA.
- Aoki-Yoshida A, Aoki R, Moriya N, Goto T, Kubota Y, Toyoda A, *et al.* 2016. Omics studies of the murine intestinal ecosystem exposed to subchronic and mild social defeat stress. *Journal of Proteome Research* **15**, 3126–3138.
- Bagot RC, Parise EM, Peña CJ, Zhang HX, Maze I, Chaudhury D, *et al.* 2015. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. *Nature Communications* **6**, 7062.
- Carrillo JA, He Y, Li Y, Liu J, Erdman RA, Sonstegard TS, *et al.* 2016. Integrated metabolomic and transcriptome analyses reveal finishing forage affects metabolic pathways related to beef quality and animal welfare. *Scientific Reports* **6**, 25948.
- Carter PA, Swallow JG, Davis SJ, Garland T. 2000. Nesting behavior of house mice (*Mus domesticus*) selected for increased wheel-running activity. *Behavior Genetics* **30**, 85–94.
- Cryan JF, Holmes A. 2005. The ascent of mouse: advances in modelling human depression and anxiety. *Nature Reviews Drug Discovery* **4**, 775–790.
- Cryan JF, Mombereau C. 2004. In search of a depressed mouse: utility of models for studying depression-related behavior in genetically modified mice. *Molecular Psychiatry* **9**, 326–357.
- Deacon RM, Croucher A, Rawlins JN. 2002. Hippocampal cytotoxic lesion effects on species-typical behaviours in mice. *Behavioural Brain Research* **132**, 203–213.
- Deacon RM, Penny C, Rawlins JN. 2003. Effects of medial prefrontal cortex cytotoxic lesions in mice. *Behavioural Brain Research* **139**, 139–155.
- Desire S, Turner SP, D'Eath RB, Doeschl-Wilson AB, Lewis CR, Roehle R. 2015. Genetic associations of short- and long-term aggressiveness identified by skin lesion with growth, feed efficiency, and carcass characteristics in growing pigs. *Journal of Animal Science* **93**, 3303–3312.
- DeWilde KE, Levitch CF, Murrrough JW, Mathew SJ, Iosifescu DV. 2015. The promise of ketamine for treatment-resistant depression: current evidence and future directions. *Annals of the New York Academy of Sciences* **1345**, 47–58.
- Dhafer R, Damisah EC, Wang H, Gruenbaum SE, Ong C, Zaveri HP, *et al.* 2014. 5-aminovaleic acid suppresses the development of severe seizures in the methionine sulfoximine model of mesial temporal lobe epilepsy. *Neurobiology of Disease* **67**, 18–23.
- Filali M, Lalonde R. 2009. Age-related cognitive decline and nesting behavior in an APPsw/PS1 bigenic model of Alzheimer's disease. *Brain Research* **1292**, 93–99.
- Fritsche E, Humm A, Huber R. 1999. The ligand-induced structural changes of human L-Arginine: glycine amidinotransferase. A mutational and crystallographic study. *The Journal of Biological Chemistry* **274**, 3026–3032.
- Golden SA, Covington HE, Berton O, Russo SJ. 2011. A standardized protocol for repeated social defeat stress in mice. *Nature Protocols* **6**, 1183–1191.
- Golden SA, Christoffel DJ, Heshmati M, Hodes GE, Magida J, Davis K, *et al.* 2013. Epigenetic regulation of RAC1 induces synaptic remodeling in stress disorders and depression. *Nature Medicine* **19**, 337–344.
- Goto T, Toyoda A. 2015a. A mouse model of subchronic and mild social defeat stress for understanding stress-induced behavioral and physiological deficits. *Journal of Visualized Experiments* **105**, e52973.
- Goto T, Kubota Y, Tanaka Y, Iio W, Moriya N, Toyoda A. 2014. Subchronic and mild social defeat stress accelerates food intake and body weight gain with polydipsia-like features in mice. *Behavioural Brain Research* **270**, 339–348.
- Goto T, Kubota Y, Toyoda A. 2015b. Plasma and liver metabolic profiles in mice subjected to subchronic and mild social defeat stress. *Journal of Proteome Research* **14**, 1025–1032.
- Goto T, Kubota Y, Toyoda A. 2016a. Effects of diet quality on vulnerability to mild subchronic social defeat stress in mice. *Nutritional Neuroscience* **19**, 284–289.
- Goto T, Tomonaga S, Okayama T, Toyoda A. 2016b. Murine depression model and its potential applications for discovering foods and farm products with antidepressant-like effects. *Frontiers in Neuroscience* **10**, 72.
- Grandin T, Shivley C. 2015. How farm animals react and perceive stressful situations such as handling, restraint, and transport. *Animals (Basel)* **5**, 1233–1251.
- Heller HC, Salehi A, Chuluun B, Das D, Lin B, Moghadam S, *et al.* 2014. Nest building is impaired in the Ts65Dn mouse model of Down syndrome and rescued by blocking 5HT_{2a} receptors. *Neurobiology of Learning and Memory* **116**, 162–171.
- Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, Bregman D, *et al.* 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 16136–16141.
- Iio W, Matsukawa N, Tsukahara T, Kohari D, Toyoda A. 2011. Effects of chronic social defeat stress on MAP kinase cascade. *Neuroscience Letters* **504**, 281–284.
- Iio W, Tokutake Y, Matsukawa N, Tsukahara T, Chohann S, Toyoda A. 2012a. Anorexic behavior and elevation of hypothalamic malonyl-CoA in socially defeated rats. *Biochemical and Biophysical Research Communications* **421**, 301–304.
- Iio W, Matsukawa N, Tsukahara T, Toyoda A. 2012b. The effects of oral taurine administration on behavior and hippocampal signal transduction in rats. *Amino Acids* **43**, 2037–2046.
- Iio W, Takagi H, Ogawa Y, Tsukahara T, Chohann S, Toyoda A. 2014. Effects of chronic social defeat stress on

- peripheral leptin and its hypothalamic actions. *BMC Neuroscience* **15**, 72.
- Íñiguez SD, Riggs LM, Nieto SJ, Dayrit G, Zamora NN, Shawhan KL, *et al.* 2014. Social defeat stress induces a depression-like phenotype in adolescent male c57BL/6 mice. *Stress* **17**, 247–255.
- Kasahara T, Takata A, Kato TM, Kubota-Sakashita M, Sawada T, Kakita A, *et al.* 2016. Depression-like episodes in mice harboring mtDNA deletions in paraventricular thalamus. *Molecular Psychiatry* **21**, 39–48.
- Kinder EF. 1927. A study of the nest-building activity of the albino rat. *Journal of Experimental Zoology* **47**, 117–161.
- Kolb B. 1984. Functions of the frontal cortex of the rat: a comparative review. *Brain Research* **320**, 65–98.
- Koyama N, Ueno Y, Eguchi Y, Uetake K, Tanaka T. 2012. Effects of daily management changes on behavioral patterns of a solitary female African elephant (*Loxodonta africana*) in a zoo. *Animal Science Journal* **83**, 562–570.
- Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, *et al.* 2007. Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* **131**, 391–404.
- Lane MD, Wolfgang M, Cha SH, Dai Y. 2008. Regulation of food intake and energy expenditure by hypothalamic malonyl-CoA. *International Journal of Obesity (London)* **32** (Suppl 4), S49–S54.
- Lang UE, Beglinger C, Schweinfurth N, Walter M, Borgwardt S. 2015. Nutritional aspects of depression. *Cellular Physiology and Biochemistry* **37**, 1029–1043.
- Lutter M, Nestler EJ. 2009. Homeostatic and hedonic signals interact in the regulation of food intake. *Journal of Nutrition* **139**, 629–632.
- Marcinkiewicz J, Kontny E. 2014. Taurine and inflammatory diseases. *Amino Acids* **46**, 7–20.
- McKim DB, Niraula A, Tarr AJ, Wohleb ES, Sheridan JF, Godbout JP. 2016. Neuroinflammatory dynamics underlie memory impairments after repeated social defeat. *Journal of Neuroscience* **36**, 2590–2604.
- Mechawar N, Savitz J. 2016. Neuropathology of mood disorders: do we see the stigmata of inflammation? *Translational Psychiatry* **6**, e946.
- Miczek KA. 1979. A new test for aggression in rats without aversive stimulation: differential effects of D-amphetamine and cocaine. *Psychopharmacology – Berlin* **60**, 253–259.
- Murakami T, Furuse M. 2010. The impact of taurine- and beta-alanine-supplemented diets on behavioral and neurochemical parameters in mice: antidepressant versus anxiolytic-like effects. *Amino Acids* **39**, 427–434.
- Nanavati SM, Silverman RB. 1989. Design of potential anticonvulsant agents: mechanistic classification of GABA aminotransferase inactivators. *Journal of Medicinal Chemistry* **32**, 2413–2421.
- Nestler EJ, Hyman SE. 2010. Animal models of neuropsychiatric disorders. *Nature Neuroscience* **13**, 1161–1169.
- Okayama T, Goto T, Toyoda A. 2015. Assessing nest-building behavior of mice using a 3D depth camera. *Journal of Neuroscience Methods* **251**, 151–157.
- Oliveira RF, Simões JM, Teles MC, Oliveira CR, Becker JD, Lopes JS. 2016. Assessment of fight outcome is needed to activate socially driven transcriptional changes in the zebrafish brain. *Proceedings of the National Academy of Sciences of the United States of America* **113**, E654–E661.
- Otahi H, Goto T, Okayama T, Kohari D, Toyoda A. 2016. Subchronic and mild social defeat stress alter mouse nest building behavior. *Behavioural Processes* **122**, 21–25.
- Otahi H, Goto T, Okayama T, Kohari D, Toyoda A. 2017. The acute social defeat stress and nest-building test paradigm: a potential new method to screen drugs for depressive-like symptoms. *Behavioural Processes* **135**, 71–75.
- Penn JK, Zito MF, Kravitz EA. 2010. A single social defeat reduces aggression in a highly aggressive strain of *Drosophila*. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 12682–12686.
- Porsolt RD, Le Pichon M, Jalfre M. 1977. Depression: a new animal model sensitive to antidepressant treatments. *Nature* **266**, 730–732.
- Potegal M, Huhman K, Moore T, Meyerhoff J. 1993. Conditioned defeat in the Syrian golden hamster (*Mesocricetus auratus*). *Behavioral and Neural Biology* **60**, 93–102.
- Rillich J, Stevenson PA. 2014. A fighter's comeback: dopamine is necessary for recovery of aggression after social defeat in crickets. *Hormones and Behavior* **66**, 696–704.
- Ruis MA, de Groot J, te Brake JH, Dinand Ekkel E, van de Burgwal JA, Erkens JH, *et al.* 2001. Behavioural and physiological consequences of acute social defeat in growing gilts: effects of the social environment. *Applied Animal Behaviour Science* **70**, 201–225.
- Ryguła R, Abumaria N, Flügge G, Fuchs E, Rütther E, Havemann-Reinecke U. 2005. Anhedonia and motivational deficits in rats: impact of chronic social stress. *Behavioural Brain Research* **162**, 127–134.
- Savignac HM, Finger BC, Pizzo RC, O'Leary OF, Dinan TG, Cryan JF. 2011. Increased sensitivity to the effects of chronic social defeat stress in an innately anxious mouse strain. *Neuroscience* **192**, 524–536.
- Schmidt M, Oitzl MS, Levine S, de Kloet ER. 2002. The HPA system during the postnatal development of CD1 mice, the effects of maternal deprivation. *Brain Research Developmental Brain Research* **139**, 39–49.
- Schubring SR, Fleischer W, Lin JS, Haas HL, Sergeeva OA. 2012. The bile steroid chenodeoxycholate is a potent antagonist at NMDA and GABA(A) receptors. *Neuroscience Letters* **506**, 322–326.
- Selye H. 1956. *The Stress of Life*. McGraw-Hill, New York, USA.
- Shen Y, Connor TJ, Nolan Y, Kelly JP, Leonard BE. 1999. Differential effect of chronic antidepressant treatments on lipopolysaccharide-induced depressive-like behavioural symptoms in the rat. *Life Science* **65**, 1773–1786.
- Sial OK, Warren BL, Alcantara LF, Parise EM, Bolaños-Guzmán CA. 2016. Vicarious social defeat stress: bridging the gap between physical and emotional stress. *Journal of Neuroscience Methods* **258**, 94–103.
- Solomon MB. 2017. Evaluating social defeat as a model for psychopathology in adult female rodents. *Journal of Neuroscience Research* **95**, 763–776.
- Steru L, Chermat R, Thierry B, Simon P. 1985. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology – Berlin* **85**, 367–370.
- Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG, Cryan JF. 2016. The neuropharmacology of

- butyrate: the bread and butter of the microbiota-gut-brain axis? *Neurochemistry International* **99**, 110–132.
- Takao K, Kobayashi K, Hagihara H, Ohira K, Shoji H, Hattori S, *et al.* 2013. Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia. *Neuropsychopharmacology* **38**, 1409–1425.
- Tasaka J, Sakai S, Tosaka T, Yoshihama I. 1989. Glial uptake system of GABA distinct from that of taurine in the bullfrog sympathetic ganglia. *Neurochemical Research* **14**, 271–277.
- Van de Weerd HA, Van Loo PL, Van Zutphen LF, Koolhaas JM, Baumans V. 1997. Preferences for nesting material as environmental enrichment for laboratory mice. *Laboratory Animals* **31**, 133–143.
- Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, *et al.* 1996. Cross-national epidemiology of major depression and bipolar disorder. *Journal of the American Medical Association* **276**, 293–299.
- Willner P. 2005. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. *Neuropsychobiology* **52**, 90–110.
- Yao W, Zhang JC, Ishima T, Dong C, Yang C, Ren Q, *et al.* 2016. Role of Keap1-Nrf2 signaling in depression and dietary intake of glucoraphanin confers stress resilience in mice. *Scientific Reports* **6**, 30659.