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

Atsushi TOYODA

1College of Agriculture, Ibaraki University, 2Ibaraki University Cooperation between Agriculture and Medical Science (IUCAM), Ami, Ibaraki, and 3United Graduate School of Agricultural Science, Tokyo University of Agriculture and Technology, Fuchu-city, Tokyo, Japan

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
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.

Table 1  Representative depression models of rodents

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

LPS, lipopolysaccharide

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.

Animal Science Journal (2017) 88, 944–952 © 2017 The Authors. Animal Science Journal published by John Wiley & Sons Australia, Ltd on behalf of Japanese Society of Animal Science.
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 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 reproducibility. 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](image-url) 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, GSK3β, 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 & Konny 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 GABAB 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-HT2A 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.

ACKNOWLEDGMENTS

I thank Drs. Mitsuhiro Furuse (Kyushu University), Tsuyoshi Okayama (Ibaraki University), Shigeru Chohnan (Ibaraki University), Daisuke Kohari (Ibaraki University), Shozo Tomonaga (Kyoto University) and Takamitsu Tsukahara (Kyoto Prefectural University) for their valuable discussions. I would also like to thank all talented members of my laboratory and various collaborators for their contributions. This research was supported in part by a Grant-in-Aid (Number 22580303) for Scientific Research (C) and Ibaraki University Cooperation between Agriculture and Medical Science (IUCAM)
(The MEXT, Japan), Prioritized Research (Ibaraki University, Japan), and the Council for Science, Technology and Innovation (CSTI) under the Cross-ministerial Strategic Innovation Promotion Program (SIP) ‘Technologies for creating next-generation agriculture, forestry, and fisheries’ (Bio-oriented Technology Research Advancement Institution, NARO) (The Cabinet Office, Japan).

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 HK, 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 heft 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. 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.

Eire S, Turner SP, D’Earth RB, Doeschl-Wilson AB, Lewis CR, Roehr 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, Leitch CF, Murrough 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.

Dhaher R, Damisah EC, Wang H, Gruenbaum SE, Ong C, Zaveri HP, et al. 2014. 5-aminovaleric 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 APPswes/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, Tonomaga 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 5HT2a 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, 16136–13141.

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, Chohnan S, Toyoda A. 2012a. Anorexibehavior 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, Chohnan S, Toyoda A. 2014. Effects of chronic social defeat stress on...
butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochemistry International 99, 110–132.

Takao K, Kobayashi K, Hagihara H, Ohira K, Shojo 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.