General and Comparative Endocrinology 280 (2019) 47–53

Contents lists available at ScienceDirect

General and Comparative Endocrinology

journal homepage: www.elsevier.com/locate/ygcen

HPA axis regulation and stress response is subject to intergenerational modification by paternal trauma and stress

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A B S T R A C T

There is increasing evidence that one's risk for psychiatric disturbances and metabolic syndromes is influenced by their parents' own health history, lifestyle and living environment. For example, paternal high fat diet is strongly linked to neuroendocrine dysregulation in offspring and increased risk for diabetes. The potential intergenerational impact of paternal stress has only just begun to emerge, with the initial evidence suggestive of greater risk for anxiety-related disorders. The hypothalamic–pituitary–adrenal (HPA)-axis is a key neuroendocrine signalling system involved in physiological homeostasis and stress response. In individuals, dysregulation of this system is closely associated with behavioral deficits and mood disorders. Various preclinical models of paternal stress have demonstrated robust behavioral shifts but little is known about the intergenerational modification of HPA axis function. This review will present evidence drawn from a range of laboratory mouse and rat models that the intergenerational influence of paternal stress on offspring behavioral phenotypes involve some level of HPA axis dysregulation. It makes the case that further investigations to comprehensively profile HPA axis function in offspring generations is warranted.

1. Introduction

The hypothalamic–pituitary–adrenal (HPA) axis is the key physiological system that regulates the stress response, and its dysregulation is widely reported in the pathophysiology of anxiety disorders, post-traumatic stress disorder (PTSD) and major depressive disorder (MDD) (see reviews by Juruena et al., 2018; Schumacher et al., 2018; Szeszko et al., 2018; Zorn et al., 2017). Perturbations of HPA axis activity have also been linked to the greater prevalence of co-morbid depression in major neurodegenerative disorders (Du and Pang, 2015). In general, pathophysiology presents as suppressed cortisol levels, enhanced negative feedback and increased sensitivity of glucocorticoid receptors, with distinct differences between PTSD and MDD (de Kloet et al., 2006; Handwerger, 2009; Yehuda, 2001). Chronic and acute traumatic stress are well-known risk factors for a spectrum of psychiatric conditions, in addition to other noncommunicable diseases (Vanitallie, 2002). Over the past decade, it has emerged that the impact of stress extends beyond the afflicted individual. There is increasing evidence that pre-and periconceptional parental stress exerts intergenerational influences on offspring behavior and physiology. The impact of maternal stress experienced before and during pregnancy on child development is well-studied (Gilles et al., 2018; Madigan et al., 2018; Simcock et al., 2018). By comparison, the impact of paternal stress on offspring mental and physical health is relatively ill-defined, and several studies have attempted to address this gap in the last decade by using a variety of animal models. This review will summarise the evidence to-date that a dysregulation of HPA axis activity and stress response underlies the intergenerational impact of a paternal history of trauma and stress on offspring risk for affective disorders.

1.1. Clinical evidence of neuroendocrine modifications linked to parental trauma

Over the past decade, there is increasing evidence that parental lifestyles and environmental exposures influence offspring neuroendocrine phenotypes and behavior. This is being increasingly evident in relation to major traumatic events. For example, in a small cohort study of 38 women who were pregnant during the events of 9/11, Yehuda and colleagues found that women who developed PTSD in response to 9/11 had lower salivary cortisol levels (Yehuda et al., 2005). Importantly, their 1-year-old infants also had comparatively lower cortisol levels, especially those who were in their third trimesters during the exposure. In a follow-up study, it was discovered that there was an inverse relationship between maternal morning cortisol levels and child behavior as infants whose mothers had lower morning cortisol levels displayed abnormal temperament embodied as poorer responses to novelty, e.g. loud noise, unfamiliar people (Brand et al., 2006). Subsequently, when these children were of preschool age, they were reported to display increased emotional reactivity and aggression behavior (Chemtob et al., 2010). These early behavioral shifts could potentially persist into

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https://doi.org/10.1016/j.ygcen.2019.04.010
Received 25 September 2018; Received in revised form 8 April 2019; Accepted 9 April 2019
Available online 11 April 2019
0016-6480/

Table 1
Collated evidence of dysregulated HPA axis stress-response and gene expression in mouse models of paternal trauma or stress.

	Model of trauma/stress exposure prior to mating	Stress eliciting exposure for F1 offspring	Offspring HPA axis profiling		Expression of HPA axis-regulating genes of offspring	Reference
			Plasma/ serum	Corticosterone responses		
Adult trauma	7-week-old male mice exposed to stress from social defeat for 10 min/ day over 10 days	6-week-old offspring subjected to 10 min of acute restraint stress	Plasma	Basal: increase in post-defeat male offspring, no differences in females	*HPA axis gene expression profiling not performed*	Dietz et al. (2011)
				5 min after stressor: no significant difference		
Early life trauma	Maternal seperation: PND1-14 for 3 h a day, coupled with dam exposed to unpredictable stress during separation	–	*Physiological stress response not studied*		Cortex: reduced CRFR2 gene expression in the female offspring, associated with decreased DNA methylation Hippocampus: increased GR gene expression in the male offspring, associated with decreased methylation of exon 1–7 at CpG3 and CpG7 Offspring have normal corticsoterone response to SSRI administration	Franklin et al. (2010), Gapp et al. (2014, 2016)
Adult acute stress	10 week old males treated with dexmethasone for 5 days	8 month old offspring subject to 20 min of acute restraint stress	Plasma	Basal: no difference between groups Immediately after removal from stressor: no difference between groups	Hippocampus: at PND 50 there was a downregulation in mRNA encoding for both the glucocorticoid receptor and mineralcorticoid receptor in offspring	Petropoulos et al. (2014)
					Hippocampus: at PND 240 there was no difference in mRNA encoding for the glucocorticoid receptor, however there was a downregulation in mRNA encoding for the mineralcorticoid receptor	
Adult sub-chronic stress	3 month old male rats exposed to 10 min of forced swimming for 21 days	–	Serum	Basal: increased in both male and female offspring of stressed males	Hippocampus: decreased glucocorticoid receptor mRNA levels in both male and females associated with increased gene methylation	Niknazar et al. (2017)
					Hippocampus: decreased glucocorticoid receptor protein in males and females with males signifcantly less than females	
Adult chronic stress	Mice exposed to 42 days of chronic variable stress throughout puberty (PN28-70)	Adult offspring subjected to 15 min of acute restraint stress	Plasma	Reduced CORT response to stress as measured by total area under the curve in both males and females compared to controls	Hypothalamus (paraventricular nucleus): microarray analysis reveals enrichment of genes involved in GR-signaling Pituitary: no change to CRFR1 or POMC1 gene expression Adrenals: no change to adrenocorticotropic hormone receptor or 11β-Hydroxysteroid dehydrogenase gene expression	Rodgers et al. (2013)
	Mice exposed to 42 days of chronic variable stress during adulthood (PN56-98)			Reduced CORT as measured by total area under the curve in both males and females compared to controls		
	Zygotes microinjected with 9 sperm miRNAs differentially expressed after chronic variable stress	14 week old offspring subjected to 15 min of acute restraint stress	Plasma	Reduced CORT response to stress as measured by total area under the curve in both males and females from miRNA microinjected zygotes compared to PBS microinjected zygotes	Pituitary: no change to CRFR1 or POMC1 gene expression Adrenals: no change to adrenocorticotropic hormone receptor or 11β-Hydroxysteroid dehydrogenase gene expression	Rodgers et al. (2015)
	Mice treated with corticosterone-supplemented drinking water from 10 to 14 weeks of age	–	*Physiological stress response not studied*		Hippocampus: in both sexes there was no difference in glucocorticoid receptor or mineralcorticoid receptor mRNA expression Adult F1 offspring are hypersensitive to acute sertraline despite no changes in serotonin receptor gene expression	Short et al. (2016), Rawat et al. (2018)

adulthood so it will be important to continue to track how these children develop in terms of their social and emotional skills.

In a separate series of studies, Yehuda and colleague also described lower mean cortisol levels in adults who had at least one parent who was a Holocaust survivor, compared to children of non-exposed parents (Yehuda et al., 2007). Interestingly, adult offspring of Holocaust survivors were themselves more likely to present with PTSD-like symptoms despite never having been exposed to such trauma (Yehuda et al., 2008), and this was specifically associated with maternal, but not paternal, PTSD. In contrast, assessments of HPA axis negative feedback regulation with the dexamethasone suppression test revealed that paternal (but not maternal) PTSD correlated with decreased glucocorticoid sensitivity in the offspring (Lehrner et al., 2014). These suggest a shift in the regulatory threshold of the HPA axis, but our current understanding of this differential physiological response is limited to only having identified differential epigenetic marks associated stress-regulatory genes. For example, a cohort study of 80 individuals who had at least one Holocaust survivor parent analysed peripheral blood mononuclear cells and found decreased gene expression of the glucocorticoid receptor (*nr3c1)*, specifically transcripts containing the Exon 1F promotor. This was attributed to a reduction in DNA methylation within that 1F promotor region (Yehuda et al., 2014). Consistent with the notion that DNA methylation is a key epigenetic modification mediating intergenerational modifications of phenotype, a smaller cohort study of 32 Holocaust survivors and 22 adult children revealed a small (~8%) increase in methylation at intron 7 of the glucocorticoid receptor co-chaperone, FK506 binding protein 51 (*fkbp5*) in the adult offspring of Holocaust survivors (Yehuda et al., 2016). While confirmatory gene expression profiling of FKBP5 was not performed in this study and since FKBP5 functions to inhibit glucocorticoid signalling, this evidence is consistent with an inhibition of GR-mediated negative feedback regulation of HPA axis activity and supports the occurrence of intergenerational epigenetic reprogramming of offspring neuroendocrinology by preconceptional paternal trauma exposure.

It has been more than two decades since the 1994 Rwandan genocide occurred that left a significant fraction of survivors with PTSD (Neugebauer et al., 2009). Epidemiological studies of that catastrophic event report that the majority of exposed youths developed signs of PTSD, which was more probable in adolescents aged 8 – 13 compared to those aged 3 – 7 (Schaal and Elbert, 2006). Many of those survivors are now young adults of child-bearing age, and studies of a potential intergenerational modification of offspring behavior and stress response have only just started to emerge. Most recently, in a study of 125 Rwandan mothers, it was reported that neither maternal PTSD nor exposure to traumatic experiences led to any significant increase in anxiety or depression in their 12-year-old children (Roth et al., 2014). Instead, it was the child's exposure to maternal-enacted family violence that drove negative mental health outcomes. However, further follow-up studies will be required to establish subsequent mental health of the children when they reach adulthood. Additionally, the potential impact of paternal PTSD or trauma exposure has yet to be examined and thus, its individual contribution to the child's behavioral phenotype remains unknown. There have been other international studies comparing the relative states of mind of offspring of war-affected adult males with and without PTSD. For example, the adolescent offspring of Croatian male war veterans with PTSD reportedly have difficulties with emotional expression and are more likely to have engage in non-suicidal self-harm or attempt suicide (Boricevic Marsanic et al., 2014a,b, 2015). It is worth noting that the instability of the family unit and deficiencies in parental care emerged as significant co-variables in this cohort. These factors would be interesting to follow-up because in a separate cohort, the presence of lower parental care or higher overprotection were linked to greater PTSD-like symptoms manifesting in the offspring of ex-prisoners of war during in the 1973 Yom Kippur War (Zerach and Solomon, 2016, 2018). However, despite the evidence of intergenerational shifts in behavioral phenotypes, the neuroendocrine status of the offspring in this series of studies have yet to be evaluated.

1.2. Offspring neuroendocrine dysfunction in preclinical models of paternal trauma and stress

The consistent revelations that a history of paternal traumatic stress correlates with the presence of behavioral abnormalities in children warrants further investigation. It remains unclear if the intergenerational impact is variable depending on the severity and chronicity of the stressor, and it would be extremely challenging to collate that extent of information for comparison across multiple human cohort studies. Furthermore, the initial evidence that GR-mediated physiological stress response is altered in offspring requires further investigation to determine the pathological origins of this dysregulation. These questions are starting to be addressed by studies of animal models of stress and our present state of knowledge will be summarised herein (see Table 1 for a summary of the limited number of studies of offspring stress response in a range of distinct mouse and rat models of paternal trauma/stress).

1.2.1. Paternal trauma (adult)

Modelling PTSD is challenging due to the heterogeneity of symptoms and numerous animal models have been developed and studied (see review by (Deslauriers et al., 2018)). The chronic social defeat stress model is one of the most commonly studied experimental mouse models of PTSD which reliably recapitulates symptoms of depression, anxiety and social withdrawal (see review by (Schoner et al., 2017)). In brief, this well-characterised mouse model typically involves exposing C57BL/6J mice to repeated daily bouts of social defeat by a larger aggressive CD-1 mouse (see Golden et al., 2011 for additional details of this protocol). In a majority of 'susceptible' animals, this leads to the defeated animal displaying marked social avoidance, anhedonia, weight loss and metabolic disturbances indicative of anxiety and depressive-like phenotypes. This experimental model was one of the first used to demonstrate the possible intergenerational modification of offspring behavior attributable to paternal trauma exposure (Dietz et al., 2011), with defeated 7-week-old male breeders siring offspring that displayed greater anxiety and depression-related behaviors compared to offspring of non-defeated breeders. Interestingly, only male offspring had a significantly higher average plasma basal corticosterone concentration compared to controls suggesting glucocorticoid insensitivity, although peak plasma concentrations of corticosterone in response to 5 min of acute restraint stress did not differ. The causes for a higher basal corticosterone concentration remain unclear, and plasma concentrations of the pituitary hormone adreno-corticotrophic hormone (ACTH) could be measured to indicate whether this dysregulation is central or peripheral in nature. A key advantage of studying a rodent model is the ability to conduct precise assessments of gene expression in discrete brain regions. In this case, the hypothalamus and hippocampus are priority regions of interest because shifts in GR/MR ratios have been reported to result in abnormal basal serum and plasma corticosterone concentrations (Deak et al., 1999; Mitra et al., 2009; Moldow et al., 2005). Follow-up studies of offspring glucocorticoid sensitivity using the dexamethasone suppression test would also complement the findings of Yehuda and colleagues regarding paternal PTSD as mentioned above.

1.2.2. Paternal trauma (early life)

Early childhood maltreatment and abuse has long-term consequences on physical health and is associated with increased risk for depression and suicide. Postnatal maternal separation is established to cause behavioral (e.g. anxiety, depression, hyperactivity) and neuroendocrine abnormalities in laboratory strains of mice and rats (Carlyle et al., 2012; Nishi et al., 2014; van Bodegom et al., 2017), although the effect size is strain-dependent (Millstein and Holmes, 2007). Several key studies of transgenerational inheritance have been

conducted using maternal separation to model early life trauma. Franklin and colleagues bred two subsequent generations of mice using male C57Bl/6J breeders that had experienced maternal separation from PND1 to 14 and were verified to have developed increased helplessness behavior, anhedonia and hypolocomotion (Franklin et al., 2010). Surprisingly, their male offspring did not display any negative behavioral phenotypes similar to their fathers. In fact, only female offspring displayed greater helplessness behavior with reduced risk-aversion. This female-specific impact is in contrast to the broad negative impacts on offspring of both sexes linked to paternal trauma experienced during adulthood. That difference suggests that the intergenerational consequences of paternal trauma on offspring are highly sensitive to age of exposure, primarily whether it occurs before or after puberty and germ cell maturation. The female offspring behavioral phenotype has been attributed to decreased methylation of the transcription initiation site of corticotrophin-releasing factor receptor 2 (CRFR2) resulting in decreased CRFR2 mRNA levels in their brains (a highly novel finding since hypomethylation is typically associated with increased gene transcription). However, studies of HPA axis activity, the physiological stress-response or glucocorticoid sensitivity have not been conducted. Another highly novel feature of this study was the description of a clear shift in the behaviors of the grand-offspring, and despite the subtle nature of those differences, this was the first clear demonstration of a paternally-mediated transgenerational impact of physical stress in any rodent model.

Follow-up studies by the same group then uncovered significant changes to the short non-coding RNA profile of epididymal sperm collected from maternal separated mice, amongst which miR-375 is implicated in stress response and metabolic regulation (Gapp et al., 2014). One identified target, miR-375, was up-regulated in the hippocampus following an injection of corticosterone to mimic the effect of stress. Additionally, it was discovered that the offspring had reduced body weights (hypermetabolism), insulin hypersensitivity and suppressed hyperglycemia after an acute restraint stress compared to controls. Subsequently, increased GR gene expression in the hippocampus of offspring was reported together with decreased DNA methylation associated with GR exon 1–7 (Gapp et al., 2016). However, methylation in the prefrontal cortex was unaltered, suggesting that the stress-induced DNA methylation modifications in germ cells do not get systematically inherited by all cells in the offspring. Interestingly, this intergenerational molecular shift was successfully reversed by intervening with environmental enrichment in the paternal generation. That indicates a unique stress-enrichment interaction since the intergenerational impact of paternal environmental enrichment alone on offspring behavioral phenotypes is minimal (Yeshurun et al., 2017). The up-regulation of hippocampal GR mRNA levels in offspring raises the possibility of altered HPA axis activity and stress response, but these studies have yet to be conducted. It would also be important to establish the expression profile of MR in the hippocampus, and extending that work to the hypothalamus. A comprehensive characterisation of the dynamic rhythm of circulating corticosterone concentrations across the day and in response to stress in the offspring would also be required. This depth of investigation is important if we are to learn how offspring stress response indirectly linked to paternal early life trauma is potentially distinct from that of individuals with an ancestral history of paternal adult trauma. These differences may be subtle, but could be crucial for understanding susceptibility and risk for stress-related diseases of future generations, at least initially in the mouse and rat models of stress before we can hope to subsequently extrapolate that knowledge to the relevant human conditions.

1.2.3. Acute stress

Dexamethasone is a synthetic GR agonist that binds with high affinity to the receptor and the DST provides a clinical assessment of HPA axis and is useful for differential diagnosis of patients with Cushing's syndrome (Ashcraft et al., 1982). It has also been used in the clinic to describe the state of HPA axis dysregulation in various psychiatric conditions, but it lacks predictive precision due to the variable rate of non-suppression even in health control groups (Mellsop et al., 1985). Its potent ability to initiate HPA axis negative feedback and strongly inhibit pituitary production of ACTH provides a means for researchers to directly manipulate HPA axis activity in rodent models of stress in order to study the intergenerational response to acute stress. One study administered 1 mg/kg dexamethasone daily on 5 consecutive days to adult C57Bl/6J male mice prior to mating (Petropoulos et al., 2014). The results revealed a novel age-dependent differences in steroid receptor expression in offspring hippocampus. In young adult male offspring (PND50), hippocampus MR gene expression was increased while GR expression was unaffected. However, in the hippocampus of 6 month old offspring, mRNA levels of MR and GR were both significantly reduced. It is possible that the onset of sexual maturation at ~PND50 is a factor in this age-specific expression pattern of GR and MR, and this could be further investigated in studies incorporating a group of castrated animals. One aspect of this model that has not been examined is the impact on offspring behavior as an indirect result of paternal dexamethasone treatment. One would predict that the robust changes in GR and MR gene expression underlie shifts in anxiety or depression-related behavioral symptoms (Rozeboom et al., 2007); these should be subject to further studies. It is also unknown if paternal dexamethasone treatment modulates similar shifts in GR/MR expression profiles for female offspring since this study only studied males; it is equally important to identify potential changes to steroid receptor expression in female brains. Surprisingly, basal plasma corticosterone concentrations were unaffected in male offspring and there was no difference in their corticosterone response to acute restraint stress. However, the rate of recovery and ability to down-regulate circulating concentrations of corticosterone post-stress was not evaluated. Non-specific DNA methylation was increased by the acute administration of dexamethasone as detected in sperm cells 60 days after the last injection, and this epigenetic modification is a shared finding in a model of paternal early life trauma from maternal separation (Franklin et al., 2010).

1.2.4. Chronic stress

In Australia, the most common reason for GP visitations is now for mental health-related issues, and the estimated lifetime prevalence of anxiety disorders is ~20% throughout the general population which far exceeds PTSD at ~7% (McEvoy et al., 2011). The most recent Stress and Wellbeing (2015) report by the Australian Psychological Society has revealed that a majority of Australians identify as being chronically stressed, with personal financial, health and family issues as the three major sources of stress. It is worth noting that young adults aged 17–25 were identified as being particularly vulnerable and 25–33% will be diagnosed with a stress or anxiety-related disorder later in life. Thus, careful and considered research into the transgenerational consequences of chronic stress is essential and more relevant to a broader spectrum of the population.

One of the first investigations into the potential intergenerational consequences of paternal chronic stress found that 6 weeks of chronic variable stress imposed throughout puberty (28 to 70 days-of-age) or in adulthood (56 to 98 days-of-age) had negative impacts on offspring behavior and HPA axis regulation (Rodgers et al., 2013). Using C57Bl/6:129 mixed-background mice, the offspring sired by mice exposed to preconceptional chronic stress had no behavioral deficiencies in the light-dark box, on the tail suspension test or with pre-pulse inhibition. There was also no cognitive impairment in the Barnes maze. Due to the absence of any striking differences in offspring behavioral phenotypes in contrast to the paternal PTSD models, it was therefore interesting that offspring were found to be hypo-responsive to stress. Both male and female offspring up-regulated plasma corticosterone concentrations after 15 min of restraint stress as expected, but these were significantly lower than controls. This difference was also present at 30 min post-

stress with the offspring of chronically stressed mice having reduced peak maximal corticosterone concentrations. All mice down-regulated corticosterone 90 min post-stress indicating an intact negative feedback response of the HPA axis, and that consistent with the absence of any deficits in pituitary CRFR1 and POMC gene expression or adrenal steroidogenic genes (Mc2r and 11βHSD-1). Rodgers and colleagues subsequently found that sperm-borne microRNAs are key to this offspring phenotype by successfully reproducing the hypo-responsive HPA axis response in mice born from embryos microinjected with sperm microRNAs isolated from chronically stressed male mice (Rodgers et al., 2015). It is worth contemplating the long-term health and survival consequences of a suppressed HPA axis for the animal, or indeed the individual human being. One possibility is that having a hypo-responsive HPA axis is a transgenerational response to a presumed stressful living environment when increased stress resilience benefits chances for survival. It would therefore be important for further assessments of how the offspring themselves physiologically and behaviorally adapt and respond to chronic stress.

In order to define the role of excessive glucocorticoid signalling associated with chronic HPA axis activation, our group mimicked daily HPA axis activation by supplementing the drinking water of adult male mice with corticosterone over a 4 week period prior to mating (Short et al., 2016). This protocol enabled significant elevations in serum corticosterone concentrations in the immediate hours of the active dark phase and suppressed their stress response, but did no impact on anxiety- and depression-related behaviors. However, paternal CORT-treatment caused the male F1 offspring to develop elevated anxiety levels. This was a sex-specific effect as the female offspring were spared from any apparent behavior discrepancies. Interestingly, we found no difference in hippocampal GR or MR gene expression that could account for the F1 behavioral phenotype. However, comprehensive profiling of their physiological stress response is still required. Instead, we found a drastic down-regulation of the paternally imprinted gene insulin-like growth factor 2 (*igf2*) that is implicated in anxiety behavior and fear memory processing (Agis-Balboa et al., 2011; Li et al., 2014; Mikaelsson et al., 2013). This down-regulation of *igf2* gene expression was also detected in their own offspring, consistent with this gene being paternally imprinted, along with the emergence of depressive behavior reflected in greater immobility in the forced-swim test. This was the first demonstration of transgenerational impacts on offspring behaviors in a model of paternal chronic stress, and an examination of corticosterone concentrations in response to forced-swim stress could potentially reveal a dysregulation of HPA axis in the F2 mice. We recently reported that both male and female F1 offspring are hypersensitive to the SSRI sertraline (Rawat et al., 2018), which could have implications for the pharmacological treatment of anxiety and depression disorders. This hypersensitivity could not be attributed to paternal CORT-treatment modulating the expression of various serotonin receptors in the offspring brains as no evidence of that was found. Further investigations examining their corticosterone response to acute SSRI administration could reveal new insights into corticosterone dependent and independent regulation of the specific F1 male offspring anxiety phenotype (Birkett et al., 2011).

Evidence of transgenerational responses to paternal stress and environmental factors exist not only humans and mice, but also for other species such as rats (Carone et al., 2010), drosophila (Ost et al., 2014) and zebrafish (Zajitschek et al., 2017). As we begin to appreciate the increasing evidence of the phenomenon of paternal transgenerational inheritance, it is essential to clarify interspecies differences in the transgenerational response since there is growing diversity in the different species used to model human health and disease. The majority of preclinical studies of paternal stress as highlighted in this review have used well-established mouse models of stress. Recent studies of paternal stress in rats have revealed some stark differences in the transgenerational molecular response. For example, Niknazar and colleagues subjected adult male rats to daily forced-swimming stress for 21 consecutive days and reported that their male and female offspring had moderate reductions in hippocampal GR mRNA and protein levels (Niknazar et al., 2017). However, the consequence of this on offspring HPA axis regulation need to be further investigated by assessing their responses to stress and subsequent recovery (higher basal serum corticosterone concentrations reported).

1.3. Discussion and future directions

Over the past decade, preclinical evidence has consistently indicated an influence of paternal stress experienced preconception on the physiology and behavior of his offspring. The behavioral pathology is generally in the domain of anxiety-related disorders, close associated with dysregulation of HPA axis activity. However, there is some level of inconsistency in the tests used to examine the behavioral phenotypes and the extent of HPA axis assessment. We would like to propose that anxiety testing should require a minimum of both the elevated-plus maze and light-dark box. Also, HPA axis profiling should at least involve GR/MR gene expression profiling in the hippocampus and hypothalamus, and provide basal, peak and post-stress recovery of serum/plasma corticosterone concentrations. It is well-known that mouse strains differ in their susceptibility and resilience to stress, as well as their behavioral responses in the most common tests of anxiety and depression-related behaviors (Barkus, 2013; Laine et al., 2018). This has to be comprehensively characterised to establish the optimal mouse strains for future studies of the physiological and behavioural stress responses, and of pharmacological and non-drug interventions. Building our knowledge of all potential outcomes associated with paternal stress across a spectrum of severities through in-depth studies of a range of animal models may help improve diagnosis and treatment of mental illness in those who are vulnerable, especially for individuals with a family history of paternal trauma. It is not impossible to envision building the capability of determining an individual's susceptibility for a specific mental illness based on their epigenomic profile, not too dissimilar to what presently done for cancer wherein certain epigenetic marks correlate with particular cancer subtypes.

More broadly, it is also essential that we endeavour to increase the diversity of our animal models, not limited to examining different substrains of a particular species, but by extending our research to other mammalian and non-mammalian species. The epigenetic regulation of intergenerational inheritance of parental traits is a topic of much research in the horticulture (Begcy and Dresselhaus, 2018) and aquaculture industries (Abdelrahman et al., 2017) in their attempts to boost yield, disease resistance, growth rate, reproductive characteristics, and tolerance to environmental stressors. Conservation efforts could also stand to gain from studies of epigenetic responses to emerging environmental stressors or infectious pathogens. An example of the latter is the highly contagious cancer, Devil Facial Tumor Disease (DFTD), which has driven Tasmanian devils (*Sarcophilus harrisii*) to the brink of extinction. Infected animals fail to mount a host-immune response to the hypomethylated tumor cells due to an absence of cell surface MHC molecules (Siddle et al., 2013) but this was successfully reversed *in vitro* by molecules that triggered a different epigenetic modification (deacetylation) in the cells, leading the authors to speculate that epigenetically modified DFTD cells may be a future vaccine to DFTD. Thus, transgenerational epigenetic studies can provide crucial information of fitness and pathogenesis to inform commercial industry practices and conservation efforts.

Acknowledgements

TYP is funded by an NHMRC project grant.

Conflicts of Interest

The authors declare no conflicts of interest

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