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Generational Patterns of Stress: Help From Our Microbes?

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Abstract

Exposure to adverse events affects the development of stress and threat response systems, and emerging evidence suggests that these effects are transmitted to future generations. How such effects are transmitted, and, similarly, how they can be ameliorated, is the topic of this article. Recent evidence demonstrates generational transmission of traits acquired following environmental exposures such as stress (e.g., parental deprivation) and dietary change (e.g., famine, high-fat diet). These diverse environmental exposures often affect both mental and physical health and appear to be transmitted through similar epigenetic and behavioral mechanisms. This convergence suggests an interesting possibility—dietary/gut-directed manipulations may work to prevent the transgenerational transmission of adversity. Although future research is required, gastrointestinal treatments show early promise in the treatment of generational mental health and are both economic and globally accessible.

Keywords

transgenerational, inheritance, stress, microbiome, probiotic, brain-gut axis

Exposure to early adversity, be it parental psychopathology, neglect, familial violence, or abuse, is one of the strongest predictors of mental (and also physical) illness across the life span (Repetti, Taylor, & Seeman, 2002). While few people dispute the fact that personal exposure to stress contributes to psychopathology risk, a more recent notion is that we may then transmit that risk to future generations (Bonduriansky, 2012). In other words, our acquired emotional traits (e.g., anxiety, depression) may be somewhat heritable. This idea of non-DNA-based inheritance is gaining support from fields as diverse as psychiatry, nutrition, and toxicology and has shown that multiple nongenomic mechanisms may be at play, from maternal behavior to germline epigenetic alterations. While understanding how and why we might be "programmed" by our ancestral experiences is critically important, so too is the appreciation for how we might outmaneuver such programming effects, which will likely require innovations in our treatments and preventions. This article begins with a discussion of some of the most recent literature demonstrating generational effects of stress on mental and physical health, before examining how one unlikely system (the gastrointestinal microbiome) may hold the key to effectively ameliorating generational risk for psychopathology.

Nongenomic Inheritance—What Is It?

Traditionally when we think of phenotypic inheritance, DNA comes to mind. Children inherit one set of genes from each parent, which come to determine their characteristics, including eye, hair, and skin color, as well as their sex and height. However, numerous instances have shown that non-gene-based characteristics and acquired traits are passed from one generation to the next. In particular, certain environmental exposures (including parent diet and exposure to stress) have been shown to program characteristics in offspring or even grand-offspring generations. For example, in the Dutch Famine cohort, maternal under nutrition during pregnancy was associated with increased body weight in those children, which was then transmitted to grandchildren in a sex-dependent fashion (Veenendaal et al., 2013).

Typically, generational effects are classed on their observed persistency. For example, intergenerational inheritance is a term often used to describe the

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transmission of behaviors/traits across one generation, from parent to child. In this instance, the individual and their gametes (which will produce the future generation) are subjected to the stressor/challenge, in effect exposing the future children themselves. The term *transgenerational inheritance*, on the other hand, is usually reserved for cases in which transmitted effects are observed in a third generation who was neither directly exposed to the stressor, nor originated from the stress-exposed gametes (see description in Curley, Mashoodh, & Champagne, 2011). This dichotomy is not just semantic; it can be used to hint at the mechanism behind the transmission. Specifically, the transmission of environmental outcomes to a third generation is often taken as evidence for the involvement of germline epigenetic changes. For example, gene transcription can be repressed through the epigenetic process of methylation, in which methyl groups are added to the DNA (Bale, 2015; Dias, Maddox, Klengel, & Ressler, 2015). Several studies have now shown that these methylation marks can escape erasure during germ cell reprogramming. Through this mechanism, future generations could experience the biological consequences of stress without direct environmental exposure. However, even in cases where stress-induced phenotypic changes are observed in a third generation, several additional non-DNA-based mechanisms may play a role. For example, a change in the maternal milieu (either biological or behavioral) can act directly on the offspring to recapitulate phenotypes across generations (see Curley et al., 2011, for greater discussion). Such maternal effects might be small and/or distant from the transferred phenotype but act to instantiate favorable conditions for its emergence. Regardless of the ultimate mechanisms, non-DNA-based inheritance highlights the importance of parents and ancestors in the transmission of mental health and illness.

Generational Transfer of Adversity—Establishing Cycles of Psychopathology

Generational patterns of psychopathology have often been reported in the literature, yet the mechanisms underlying such patterns are still being elucidated. Within maternal transmission models, heritability is observed for several parenting behaviors. For example, rhesus macaque females abused as infants are more likely to go on to abuse their own offspring (Maestripieri, 2005). Similarly, natural variations in the quality of rodent maternal behavior remain consistent across generations, but environmental stress/enrichment can initiate or terminate (respectively) low-quality care patterns (Champagne & Meaney, 2006, 2007; Francis, Diorio, Liu, & Meaney, 1999). Maternal stress is also known to program the hypothalamic-pituitary-adrenal (HPA) axis. In humans, blunted cortisol responses were observed in mothers with PTSD and their babies following exposure to the September 11 World Trade Center attacks in New York City (Yehuda et al., 2005). In developing rodents, behavioral stress responses and HPA axis reactivity are elevated following maternal stress exposure (Bale, 2015). Such maternal stress experience also affects cognitive functioning and development of threat response systems in rat pups. For example, maternal preconception stress has been shown to accelerate the maturation of threat response behaviors in infant rats, leading to better retention of learned associations without affecting overall anxiety levels (Kan, Callaghan, & Richardson, 2016). Such accelerated development could conceivably prepare the infant for coping in future high stress environments, but could be maladaptive in future environments characterized by low stress.

Paternal stress exposure also can impact stress reactivity and threat learning in the offspring. In rodents this is especially interesting, as fathers do not play an active caregiving role. Hence, paternal transmission rodent models are often used to examine the possibility of germline epigenetic inheritance, or a maternally mediated paternal effect. In one of the first illustrations of patrilineal stress transmission, Franklin and colleagues (2010) demonstrated that chronic and unpredictable stress in the rearing environment increased the expression of depressive and anxious behaviors in exposed males, as well as in their female offspring (F1 generation). It is interesting that F1 males transmitted the phenotype to the grand-offspring males (F2), despite not showing the behavior themselves. These authors also observed epigenetic changes in sperm and brain sites that persisted across generations, suggesting that methylation of germ cells might be the mode of transmission. The effects of stress on the peripheral nervous system may also be transmissible, as both glucose metabolism and insulin sensitivity were inherited in this stress model (Gapp et al., 2014). We recently showed that early life stress (maternal separation) induced accelerated development of threat circuitry in directly exposed males, as well as their male offspring and grand-offspring (Callaghan, Cowan, & Richardson, 2016), adding to the literature demonstrating that even adversities limited to a father's infancy can have generational outcomes. In another study, paternal preconception exposure to specific learned associations (odor-shock pairings) increased both the behavioral sensitivity toward and the neural space dedicated to processing that particular odor in the offspring (Dias & Ressler, 2014). In that study, germline methylation patterns in the sperm were observed in genes

associated with processing the exposed odor, and replacing natural mating with in vitro fertilization (IVF) did not change the biological and behavioral outcomes, suggesting that the effect was not maternally mediated (i.e., the mother never came into contact with the father). However, other studies have observed an almost complete ablation of stress-related brain and behavioral inheritance patterns following IVF (Dietz et al., 2011), suggesting that maternal mediation of paternal effects is also a viable pathway for some transmitted outcomes.

While such studies paint a complicated and somewhat grim picture of generational mental health, it is important to recognize that the prenatal or postnatal environment can mitigate parental exposure effects. For example, the differential allocation hypothesis states that mothers will alter their investment in offspring as a function of the perceived fitness of a male, reducing her investment in offspring derived of low-quality or undesirable mating pairs. A corollary is the compensation hypothesis in which mothers may actually increase their investment and care of offspring from low-quality males to counteract the effects of the detected paternal deficit (Curley et al., 2011). These two possibilities can play out in the prenatal period, in the postnatal period, or both, and might override or account for apparent paternally associated effects on offspring development. A particularly nice example of such maternally mediated paternal effects showed that female mice engaged in higher quality care toward offspring from environmentally enriched males than from standard lab housed males (arguably an impoverished environment), which then resulted in faster growth of the paternally enriched offspring (Mashoodh, Franks, Curley, & Champagne, 2012). In that paradigm, father anxiety was negatively correlated with maternal care behavior, suggesting that paternal anxiety expression might have been an important variable involved in the induction of maternal behavioral change. Whether and how mothers change their rearing investment during the prenatal period in this model remains to be determined.

Diet, Stress, the Microbiome, and Psychopathology

While numerous studies have examined how stress and adversity effects are passed down through generations, a concurrent body of literature has been investigating the generational effects of diet and microbial changes on offspring body composition and threat reactivity. Such studies suggest that stress/adversity as well as dietary/microbiome changes act in comparable ways to influence physical and mental health across generations.

Several studies have documented the diverse array of physical and mental health outcomes associated with the ancestral experience of famine, from coronary heart disease (Painter, Roseboom, & Bleker, 2005) and obesity (Veenendaal et al., 2013), to neurodevelopmental disorders (Susser, Hoek, & Brown, 1998) and schizophrenia (Hoek, Brown, & Susser, 1998). Even variations in diet that we commonly observe across the world today, such as fat consumption, appear to influence the physical and mental health of offspring, which then reverberates across generations. For example, exposure to high-fat diet (HFD) during the rodent postweaning period, or during pregnancy, increased maternal weight and plasma insulin during pregnancy and was associated with fetal changes in insulin levels, inflammation, and body weight that persisted across postnatal development (Chang, Gaysinskaya, Karatayev, & Leibowitz, 2008; Grayson et al., 2010; Srinivasan, Katewa, Palaniyappan, Pandya, & Patel, 2006). Maternal HFD is also associated with sex-specific increases in anxious behaviors in infant offspring, as well as altered serotonergic system development (Sullivan et al., 2010). Maternal HFD induced effects can also be transmitted to subsequent generations through the paternal line. For instance, Dunn and Bale (2011) showed that maternal HFD during pregnancy was associated with increased body size in females across three generations, but the effect was carried through the fathers, inherited through a set of paternally imprinted genes. The paternal diet is itself also a direct regulator of offspring health with HFD rodent fathers producing female progeny with β-cell dysfunction, insulin sensitivity, and impaired glucose tolerance (despite those females being of normal weight; Ng et al., 2010). In morbidly obese humans, men who lost weight due to bariatric surgery exhibited extensive remodeling of sperm DNA methylation in gene loci important for appetite control (Donkin et al., 2016).

Just as diet affects both physical and emotional health, so too does exposure to stress/adversity. As discussed in the previous section of this article, psychosocial stressors have a generational impact on offspring threat and stress reactivity and the development of those systems. Many experimental procedures used to elicit psychosocial stress in the rodent (e.g., maternal separation) also act to model the development of physical health problems, such as functional gastrointestinal disorders (e.g., irritable bowel syndrome; O'Mahony et al., 2009). Maternal separation in monkeys also produces disturbances in the gastrointestinal microbiome (i.e., the bacterial community living in the gut; Bailey et al., 2011). In mice, the microbiome was shown to be essential for the depressive and anxiety disturbances

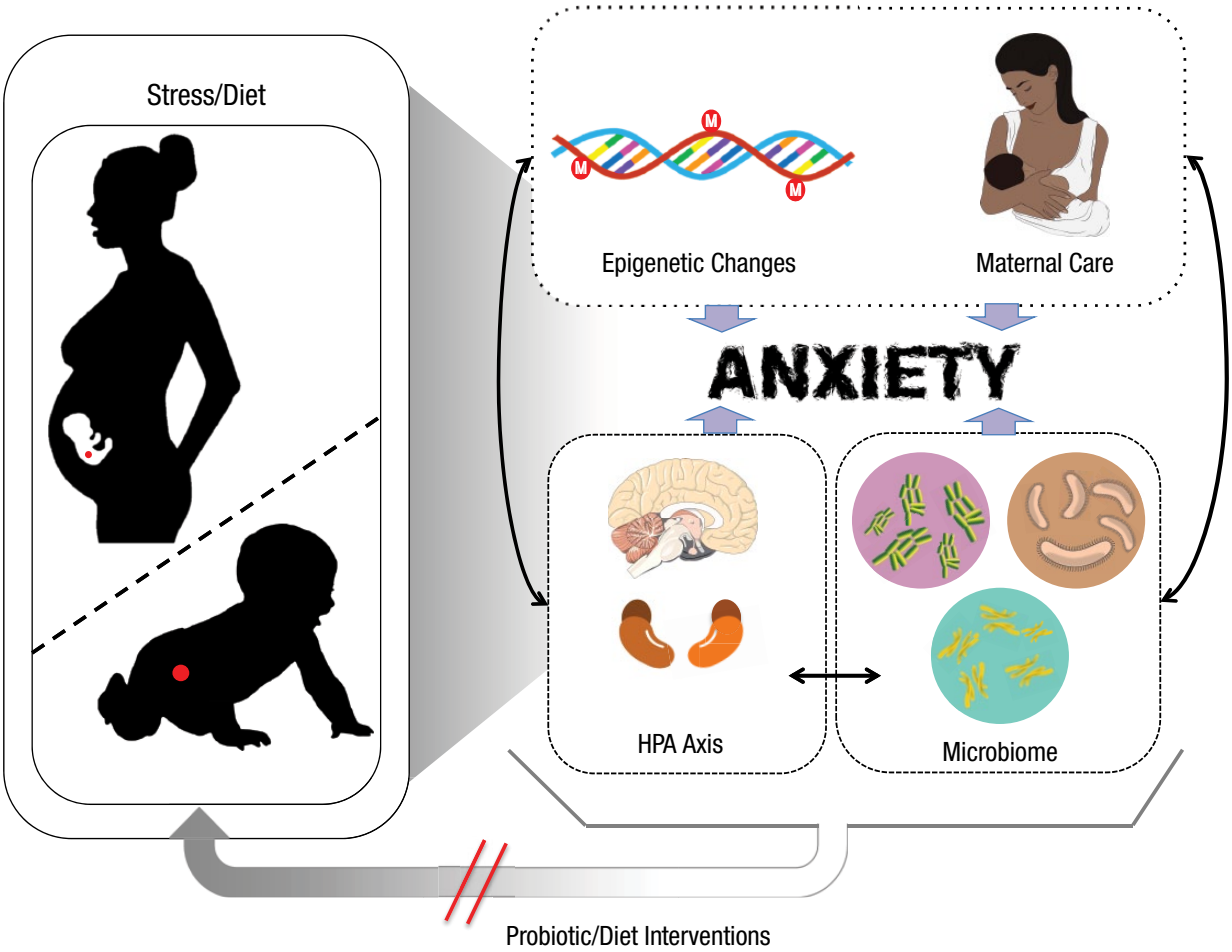

Fig. 1. A model of potential mechanisms via which prenatal or postnatal stress, and/or dietary alteration, leads to phenotypic change in future generations. Environmental exposures are likely to affect epigenetic machinery, which could change maternal behavior in such a way that anxious responses emerge in offspring, and/or alter the expression of genes in germ cells that are important for development of offspring anxiety. Epigenetic changes and maternal care can impact the functioning of the HPA axis, influencing stress reactivity, as well as select for particular microbiome states that are important for anxious responding. Microbiome and HPA axis both influence each other and are themselves affected directly by stress/dietary experiences and could thus feedback to influence epigenetic states and shape maternal (or parental) care. Probiotic or dietary manipulations may represent one intervention point to stop generational cycles of adversity.

associated with maternal separation, as such disturbances were not observed in maternally separated mice lacking a microbiome (i.e., in germ free mice; De Palma et al., 2015). Furthermore, the community composition of the gastrointestinal microbiome has been shown to be at least partly heritable in human twin studies (Goodrich et al., 2016), suggesting that the microbiome might play a role in selecting for anxious behavior across generations. Whether community-level microbiome disruptions produced by stress are handed down to successive generations is an open question. Furthermore, whether germline epigenetic alterations, or maternal investment, work to select specific microbiome community structures needs to be examined (see Fig. 1). Regardless, the data that currently exist raise an intriguing question: Can diet and microbial alterations be leveraged to treat (and ultimately halt) the generational transfer of stress?

Treating the Gut Following Psychosocial Stress—A Solution for Future Generations

Studies using dietary or microbial manipulations to treat the generational effects of stress have been surprisingly scarce. In nongenerational studies, dietary interventions (micronutrient supplementation) have been shown to reduce immediate and long-term depression symptoms following a natural disaster trauma in adults (Rucklidge, Blampied, Gorman, Gordon, & Sole, 2014).

In generational studies, dietary interventions have also been shown to prevent the transmission of stress effects across generations. For example, moderate preconception paternal calorie restriction (25% reduction) decreased anxiety behavior in adult offspring (Govic, Penman, Tammer, & Paolini, 2016). We recently examined whether probiotic supplementation during maternal separation would prevent behavioral alterations related to threat system development in exposed pups and their future offspring. We observed that a probiotic compound (*L. rhamnosus* and *L. helveticus*) administered across the separation period reverted the behavior of stress-exposed rats back to a nonstressed phenotype (Cowan, Callaghan, & Richardson, 2016), and prevented the transmission of stress-altered threat system development to the next generation (Callaghan et al., 2016). Previous studies had shown that the same probiotic treatment reversed corticosterone changes produced by maternal separation stress (Gareau, Jury, MacQueen, Sherman, & Perdue, 2007), suggesting that the probiotic might be working at the level of stress hormones to affect change in the threat response system. Hence, gastrointestinal manipulations might help to tone the HPA axis and threat reactivity to reduce anxious behavior, which might then create a feed-forward loop to affect anxiety across successive generations (see Fig. 1). Such feedback may also occur at an epigenetic level. For example, transgenerational effects on obesity can be ameliorated by maintaining rodents on a diet rich in methyl donors, which increases methylation at genetic loci important for appetite control (Waterland, Travisano, Tahiliani, Rached, & Mirza, 2008).

Clinical Implications and Future Directions

The studies discussed above are a promising start for examinations of dietary and probiotic interventions for generational effects of stress, but more work is required, especially on probable mechanisms. In particular, understanding the interaction between stress and diet, the microbiome, HPA axis, epigenetic mechanisms, and maternal care is ripe for investigation. Similarly, understanding how symptomatic change in nutrition associated with mental illness (e.g., depression) feeds back to maintain symptoms across generations is essential. In spite of these outstanding questions, researchers should be encouraged by the clinical relevance of the findings. Specifically, demonstrating that mental well-being may begin with gastrointestinal health has significant implications for microbiome-based preventions and treatments that could be both cost-effective and made almost globally accessible.

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Declaration of Conflicting Interests

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