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Review

Epigenetics and the origins of paternal effects ☆

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ABSTRACT

Though there are multiple routes through which parents can influence their offspring, recent studies of environmentally induced epigenetic variation have highlighted the role of non-genomic pathways. In addition to the experience-dependent modification of DNA methylation that can be achieved *via* mother–infant interactions, there has been increasing interest in the epigenetic mechanisms through which paternal influences on offspring development can be achieved. Epidemiological and laboratory studies suggest that paternal nutritional and toxicological exposures as well as paternal age and phenotypic variation can lead to variations in offspring and, in some cases, grand-offspring development. These findings suggest a potential epigenetic germline inheritance of paternal effects. However, it may be important to consider the interplay between maternal and paternal influences as well as the experimental dissociation between experience-dependent and germline transmission when exploring the role of epigenetic variation within the germline as a mediator of these effects. In this review, we will explore these issues, with a particular focus on the potential role of paternally induced maternal investment, highlight the literature illustrating the transgenerational impact of paternal experiences, and discuss the evidence supporting the role of epigenetic mechanisms in maintaining paternal effects both within and across generations.

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The study of parental influences, in both epidemiological and laboratory contexts, suggests that there are diverse pathways though which parents can shape their offspring's development. In mammals, the intense prenatal and postnatal investment of mothers in the care of their offspring and the rarity of bi-parental care have directed much of the research on parental effects to the role of mother–infant interactions in promoting survival and adaptive development. However, even among species in which paternal investment in offspring care is limited, there is evidence for paternal effects. Within the literature, "paternal effects" on development can have a variety of meanings. In addition to describing the influences of male care-giving in species where bi-parental or exclusively paternal care is observed (*e.g.* marmosets, prairie voles, *Peromyscus californicus*), this term can also refer to inheritance of genes through the patriline which exhibit parent-of-origin expression patterns (*i.e.* imprinted genes that are expressed exclusively from the father such as *Peg1* & *Peg3*), or the influence of genes expressed on the Y chromosome that can exert effects on male brain and behavioral development independent of the effects of *Sry* on hormonally regulated sexual differentiation. More recently, there has been increased interest in

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exploring the observation that the life-history experiences of males (*e.g.*, nutrition, toxin exposure) can influence the development of both their male and female offspring. These observations, coupled with advances in our understanding of the persistence of environmentally induced epigenetic modifications, has lead to speculation regarding the germline transmission of environmental experiences and a re-evaluation of the concepts inherent in Lamarckian theories of the inheritance of acquired traits. Though this inheritance system would not be predicted to occur exclusively in the patriline, the information transmitted *via* sperm during the process of fertilization is thought to be limited to genetic/epigenetic material, whereas the maternal oocyte contributes both genetic/epigenetic factors and a cellular environment which can regulate the activity of those factors, thus making it difficult to separate the unique contribution of maternal epigenetic modifications. Thus, the study of environmentally induced paternal germline epigenetic effects is currently expanding and may provide an explanation for the transgenerational influence of father's experiences on offspring development. However, we propose that there are important experimental design issues that must be considered when exploring the mechanisms of paternal effects. In particular, it is important to consider the distinction between effects on a germ cell *vs*. the primordial germ line, the number of generations an effect must persist to be considered a germline transmission, and the possible interplay between maternal and paternal effects that may moderate or mediate the occurrence of paternal effects. In this review, we will highlight the studies in humans and animals that indicate an inheritance of paternal experiences, discuss the theoretical pathways through which these effects may be achieved, and discuss the role of epigenetic mechanisms in mediating paternal influences.

Paternal nutrition: influences across generations

Large-scale epidemiological studies have established that the diet and nutritional status of fathers and grandfathers can exert transgenerational effects on the phenotypes of sons and grandsons, with particular influences on metabolic functioning. For instance, archival data indicate that food availability during the pre-pubertal slow growth phase (8–12 years of age) of grandfathers is associated with the risk of diabetes and cardiovascular disease as well as mortality in grandsons but not granddaughters (Kaati et al., 2002; Kaati et al., 2007; Pembrey et al., 2006). In rodents, changing the quantity or quality of a male's diet at various developmental time points has also been found to induce phenotypic changes in male offspring. For example, males exposed to prenatal dietary restriction (through reductions in caloric intake of their mother during late gestation), who are then fed *ad libitum* throughout the rest of their life, sire offspring with reduced birth weights and impaired glucose tolerance compared to fathers who were born to control dams (Jimenez-Chillaron et al., 2009). Restricting the caloric intake of males prior to mating can also lead to altered metabolic functioning of offspring. Males exposed to a single 24 hour period of food deprivation 2 weeks before they were mated were found to have offspring with reduced serum glucose and altered levels of corticosterone and IGF1 compared to males who did not fast at this time point (Anderson et al., 2006). The nutrient composition of food intake may also have consequences for future generations. For instance, the chewing of betel nuts (which contain nitrosamines) is very popular across Southeast Asia and Polynesia, and individuals who do this are known to be at an increased risk of developing metabolic syndrome (Lin et al., 2008). Interestingly, it has been recently demonstrated that the duration and quantity of betel nut intake by males is positively related to the risk of their own offspring developing metabolic syndrome (Chen et al., 2006). Significantly, this finding has been confirmed in a mouse study, with offspring sired by males who were exposed to betel nuts in their diet prior to mating being at an increased risk for developing hyperglycemia (Boucher et al., 1994). Moreover, the inheritance of this phenotype can be transmitted for at least three generations. Increased body length and reduced insulin sensitivity have also been observed among mice born to dams fed a high-fat diet from preconception to the weaning period (Dunn and Bale, 2009) and offspring and grand-offspring of rat dams fed a low protein diet during gestation have elevated hypertension, despite both these generations being fed control diets (Harrison and Langley-Evans, 2009). In both of these studies, the induced phenotypes were transmissible to the next generation *via* either the male or female line. Overall, these studies indicate that dietary effects, achieved through both quantity and quality of food intake, can induce effects on male phenotype that may be inherited by subsequent generations.

Exposure to drugs, toxins, and endocrine disruptors

Epidemiological studies have demonstrated that the exposure of fathers to various drugs, toxins, and other chemicals, such as endocrine disruptors, before mating is associated with altered behavioral development in their children, even after accounting for other potential confounding lifestyle variables. For instance, the early onset of paternal smoking is related to greater body mass index of sons (Pembrey et al., 2006), whereas paternal alcoholism is associated with reduced birth weight in offspring (Little, 1987). Interestingly, children of alcoholic fathers exhibit hyperactivity and reduced cognitive performance, but only if the alcoholic father is also their biological father, demonstrating the potential for these induced effects being preconceptual in nature (Hegedus et al., 1984; Tarter et al., 1984). Laboratory studies of these alcohol-induced effects have indicated that exposure of male mice and rats to alcohol has numerous effects on their offspring, including reduced litter size, reduced birth weight, developmental retardation, increased mortality, and compromised immunity as well as behavioral deficits such as impaired discrimination on spatial tasks and altered aggressive, risk taking, and anxiety-like behavior (Abel, 2004; Abel and Tan, 1988; Abel and Bilitzke, 1990; Ledig et al., 1998; Meek et al., 2007; Wozniak et al., 1991). These effects have been established both with males who were exposed to alcohol until the time of mating and also with those males who have had withdrawal periods of various lengths prior to mating. Likewise, cocaine-exposed fathers sire offspring with impairments on tests of visuospatial attention, spatial working memory, and spontaneous alternation and have reduced cerebral volume (Abel et al., 1989; He et al., 2006). Males exposed to various other drugs and toxins such as opiates, cyclophosphamide, ethylene dibromide, and lead have been found to sire offspring with developmental and behavioral impairments, with these effects in several cases being transmissible *via* the male line to second and third generations (Hales and Robaire, 2001). The severity of these effects is related to the duration and dosage of drug/toxin exposure as well as the developmental period when paternal exposure occurred (though in most of these studies, males are exposed post-weaning). Though there are species differences and sex-specific consequences of these effects, overall, these studies provide strong evidence that the exposure of males to drugs and other toxins can lead to behavioral changes in offspring, likely *via* the paternal germline.

Endocrine disruptors, such as the anti-androgenic compound vinclozolin, are another class of pharmacological agents that can induce altered development in the offspring of exposed fathers. However, in contrast to the previous examples, in order for this paternal transmission to occur, males must be exposed within a critical period late in their own embryogenesis during gonadal sex determination (Anway and Skinner, 2008). Hence, rat dams who are exposed to vinclozolin during late gestation, have offspring who are at an increased risk of tumor formation, kidney disease, immune abnormalities, and infertility, phenotypes which are observable for at least four subsequent generations through the male line but are not transmissible through the female line (Anway et al., 2005; Anway et al., 2008; Anway and Skinner, 2008). Moreover, sex-specific changes in anxiety-like behavior are observed in offspring that were separated from the originally exposed dam by as many as four generations through both the male and female lines