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Montgomery, W. I. (2021). Molecular mechanisms of self-regulation in multiannual rodent populations: Experimental test of an updated hypothesis. *Journal of Animal Ecology*, *90*(4), 780-783. https://doi.org/10.1111/1365-2656.13458

Published in:
Journal of Animal Ecology

Document Version:
Publisher's PDF, also known as Version of record

Received: 17 February 2021 | Accepted: 23 February 2021

DOI: 10.1111/1365-2656.13458

IN FOCUS

Journal of Animal Ecology BRITISH ECOLOGICAL SOCIETY

Molecular mechanisms of self-regulation in multiannual rodent populations: Experimental test of an updated hypothesis

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Handling Editor: Jennifer Gill

Abstract

In Focus: Edwards, P. D., Frenette-Ling, C., Palme, R., & Boonstra, R. (2021). Social density suppresses GnRH expression and reduces reproductivity in voles: A mechanism for population self-regulation. *Journal of Animal Ecology*, *90*, 784–795. Intrinsic population processes are important in the regulation of populations of small rodents, including those which display multiannual cycles. By measuring reproductive parameters, faecal androgen metabolites, and gene expression and DNA methylation in the CNS of juvenile voles, this paper demonstrates that suppression of reproduction occurs in female voles at high density compared to low density in enclosures, and that this maternal, epigenetic effect is also apparent in their offspring. This suggsests that direct density dependence influences reproduction and, hence, immediate rate of population growth, while gene expression mediated by DNA methylation blocking transcription, may have a delayed density-dependent effect in juveniles. Both direct and delayed density dependence are necessary to generate multiannual population cycles. Edwards et al. (2021) break new ground in demonstrating the molecular and physiological basis of variation in population dynamics of small mammals ranging from multiannual cycles to stability that have fascinated researchers for nearly a century.

KEYWORDS

DNA methylation, gene expression, multiannual cycles, population, reproductive suppression, rodent, self-regulation

The insights of Charles Elton (1924, 1942) concerning historical cycles of abundance in herbivores, especially small rodents and lagomorphs, initiated a major area of interest within the then, new discipline of animal ecology. This early work was based largely on natural history with a theoretical foundation describing predator–prey cycles provided by Lotka (1925) and Volterra (1926). What limits or regulates population size and the causes of multiannual cycles in abundance, particularly in voles and lemmings, have been unresolved questions in ecology for nearly 100 years. Krebs (2013) and Oli (2019) expertly reviewed the copious literature while Andreassen et al. (2020) also identified 10 key remaining questions. Edwards et al. (2021) present new findings on population regulation in small rodents, addressing the most crucial of the questions posed by Andreassen et al. (2020), the control of reproduction and delays in population recovery. Reproduction drives the population growth phase but it is not clear, for example, what controls the start of reproduction, how long a breeding season lasts, that is, what brings a season to an end, or how many litters or offspring per litter a female gives birth to.

One of the weaknesses in population models is the frequent lack of detail provided on the biological mechanisms underpinning supposedly important population processes (Krebs, 2013). A change in abundance may be inferred but we remain uncertain about what is

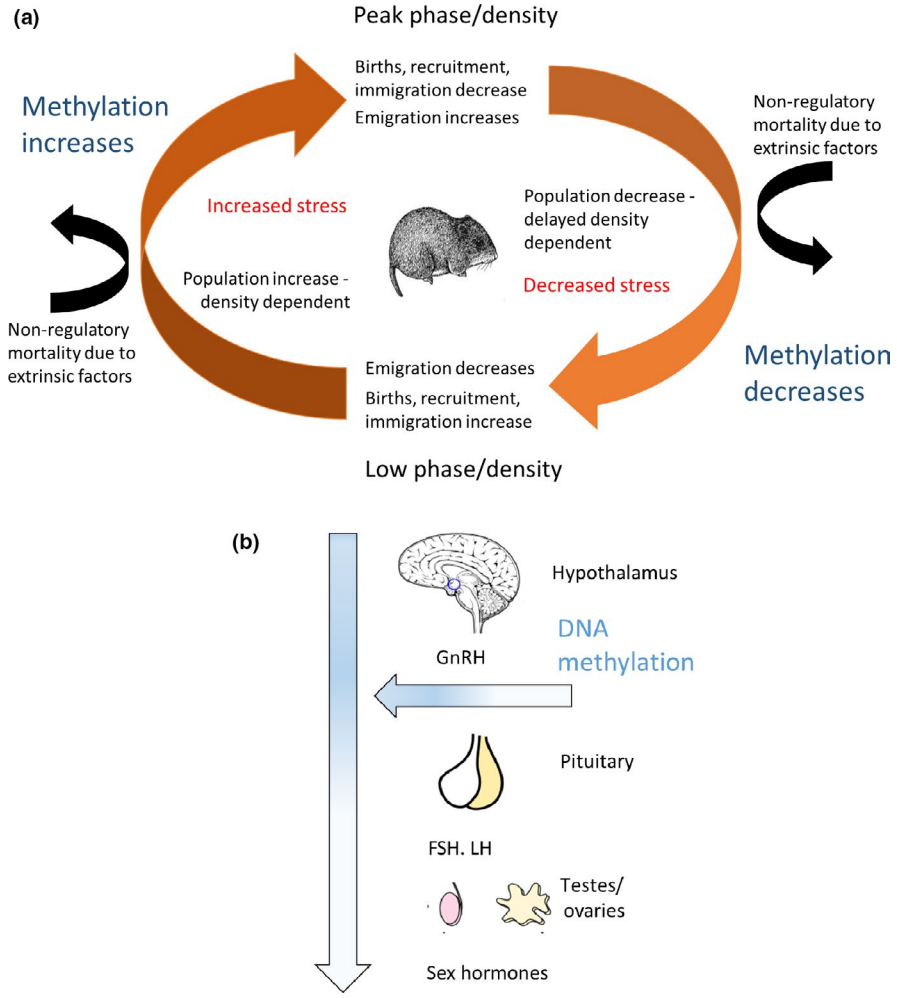

FIGURE 1 (a) Putative model of population self-regulation in a small rodent mediated by DNA methylation supressing transcription of GnRH. Upward and downward brown arrows indicate population growth and decrease, respectively. The cycle involves a peak and low phase which may be annual or span a number of years and involve more than one generation. Increased methylation is associated with increased stress as density increases. Non-regulatory mortality (black arrows) involves multiple extrinsic factors which may track population density or effect large losses but do not drive population size in a predictable direction. (b) Diagrammatic, simplified hypothalamus, pituitary, gonadal axis controlling the production of testosterone and oestrogen in mammals. GnRH is gonadal releasing hormone which is under genetic control. Transcription is controlled epigenetically by increased DNA methylation at some cytosine positions on a base sequence which supresses production of GnRH and, hence, sex hormones that control development and ultimately reproduction. Methylation level is increased by environmental factors. Genes do not change but epigenetic changes can be transferred through the female line. Epigenetic changes may be permanent, lead to genetic mutations, or demethylation may occur

happening and why. While this may be an adequate approach in constructing and testing a model, it remains unsatisfactory as a means to understanding the evolution and great diversity of biological processes. Edwards et al. (2021) not only examine the potential role of reproductive inhibition in population cycles but they also delve into its mechanism by examining associated hormones involved in stress and reproductive physiology, as well as the mechanism governing gene expression of hormone release factors in areas of the brain of young voles associated with maternal behaviour and responses to high population density. While the long-standing hypothesis that multiannual cycles are driven by changes in genotype frequency is no longer supported (Boonstra & Boag, 1987; Chitty, 1960, 1971), Edwards et al. (2021) support the novel idea that suppression of transcription to block genetic expression is a key.

Non-pregnant, wild caught, adult Meadow voles *Microtus pennsylvanicus*, were introduced into predator-proofed enclosures (25 m square) at the start of the vole breeding season in May of 3 years, at high (20–24 per enclosure) or low (4–6 per enclosure) density. Their numbers and reproductive condition were monitored using single individual, live traps, until the end of August, when all voles were removed such that each population was short-lived and did not continue from one year to the next. Faecal androgen metabolites (FAM) were assayed to discriminate reproductive and non-reproductive individuals using faeces recovered from traps. Immature (juvenile) voles removed at the end of each replicate were available to investigate expression of two candidate genes associated with hypothalamus and the medial amygdala, areas of the brain which are implicated in processing social stimuli, olfactory cues and defence

and reproductive behaviour (Spitieri et al., 2010). The first candidate gene, GnRH1, is implicated in the stress hormone pathway of the hypothalamic–pituitary–gonadal axis, and the second, ESR1, encodes for an oestrogen receptor associated with parental behaviour and aggression. Thus, Edwards et al. (2021) test a very specific process that controls regulation of social behaviour and reproduction and, potentially, plays a central role in population regulation in small mammals.

At high density, FAM levels were low and female reproduction including lactation were depressed in comparison with low-density enclosures. GnRH levels were low in voles from high-density enclosures. This was related to high levels of DNA methylation in female voles but not males which suggests that epigenetic effects in females may explain the heritability of supressed reproduction. These results are consistent with the view that female reproduction is a key in regulating population size in small rodents with direct negative feedback from increased density, and delayed density-dependent effects through a heritable epigenetic process involving DNA methylation. Methylation is triggered by environmental cues and is reversible so that changes in population size track immediate and past density, that is, direct and delayed density dependence that population theory suggests generates multiannual population cycles.

Studies involving small mammals especially those at higher latitudes are not without their frustrations. Datasets need to be long enough to apply time series and related analyses; indices of abundance may not reflect density adequately; harsh winter conditions prevent access to animals; estimating rodent food resources, and abundance of predators and prey simultaneously is challenging; and spatial scale of studies can range from a few metres to continental expanses. The effort required to test hypotheses under field conditions is considerable and the results may confound and confuse (Krebs, 2013). This does not mean that the intense research effort of those engaged in this area of research has been wasted. Quite the reverse. We have learnt much about the value of hypothesis testing and experimental studies and the application of new techniques (Krebs, 1996, 2013) and how dynamics vary over time and space and between and within species (Bjornstad et al., 1998, 1999). We recognise the importance of bottom up/top down processes involving resource quality and consumption (Erlinge et al., 2011; Prevedello et al., 2013) and mortality and non-lethal effects of specialist and generalist mammalian and avian predators (Korpimäki & Norrdahl, 1998; Sundell, 2006; Ylönen & Ronkainen, 1994). Ecological and epidemiological insights have come out small mammal studies on the compounding effects of pathogens and parasites (Kallio et al., 2015; Ostfeld, 2015; Smith et al., 2009). Intrinsic changes in genotype and phenotypic changes in behaviour and physiology have long been recognised as potential self-regulatory processes (Boonstra & Boag, 1987; Chitty, 1960, 1971), directly or indirectly influencing population growth and decrease. Initially, self-regulation focussed on stress and aggression in males, but more recent interest is related to female territoriality, reproduction and defence from infanticide (Wolff, 1997), and stress-related, maternal effects influencing reproduction in offspring (Bian et al., 2015).

Multifactor models, where two or more factors interact to produce population cycles, are in the ascendancy with increased interest in experimental tests involving two or three factors (Krebs, 2013). There is a strong argument in favour of including a combination of extrinsic and intrinsic population processes in these tests, as it seems increasingly evident that there must be a central role for self-regulation, involving direct as well as delayed density dependence, effectively limiting population growth or initiating population decline (Boonstra et al., 1998; Lambin & Yoccoz, 1998; Oli, 2019; Ostfeld et al., 1993; Wolff, 1997). The central role of self-regulation is strongly supported by studies which show continued population decline where predators are absent or food is abundant (Edwards et al., 2021; Oli, 2019) (Figure 1). Seasonality and winter harshness and duration may or may not determine periodicity and amplitude of cycles which varies with latitude. There is no overarching consensus regarding the extrinsic drivers of population change, with a reliance on case studies, although the complexities of the ecological processes leading to a wide range of dynamics in rodents and other small mammals remain a source of fascination (Krebs, 2013; Oli, 2019).

It is arguable that the elegant physiological and genetic processes described by Edwards et al. (2021) are sufficient to explain population regulation in annual and multiannual rodents. It is also arguable that such a mechanism is found in many mammals. Edwards et al. (2021) urge caution, recognising the potential role of many genes as well as the need to verify changes in gene expression in natural populations. Further experimental studies directed at defined mechanisms, such as Edwards et al. (2021), and wider comparative studies focussing on variation in reproductive characteristics such as age of maturation and length of breeding season in multiannual and annual species, will ensure that the limitation and regulation of small mammal populations remain innovative and rewarding areas of population ecology.

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How to cite this article: Ian Montgomery W. Molecular mechanisms of self-regulation in multiannual rodent populations: Experimental test of an updated hypothesis. *J Anim Ecol*. 2021;90:780–783. https://doi.org/10.1111/1365-2656.13458