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NEWS AND VIEWS

PERSPECTIVE

Masterpiece of epigenetic engineering – how *Toxoplasma gondii* reprogrammes host brains to change fear to sexual attraction

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The protozoan parasite *Toxoplasma gondii* is known to induce specific behavioural changes in its intermediate hosts, including humans, that are believed to increase the chance of its successful transmission to the definitive host, the cat. The most conspicuous change is the so-called fatal attraction phenomenon, the switch from the mice's and rats' natural fear of the smell of cats toward an attraction to this smell. The mechanism of this manipulation activity is unknown; however, many indices suggest that changes in the concentrations of dopamine and testosterone are involved. In this issue of Molecular Ecology, Hari Dass & Vyas (2014) present results of a study showing that, by hypomethylation of certain regulatory elements of key gene, *Toxoplasma* is able to reprogramme the brain's genetic machinery in such a way that cat odour activates and changes the wiring of the medial amygdala circuits responsible for sexual behaviour. This study delivers the first clear evidence of a parasite's ability to use sophisticated epigenetic engineering techniques for the manipulation of the phenotype of its infected host.

Keywords: epigenetics, evolutionary parasitology, gene expression, manipulation hypothesis, methylation, testosterone, toxoplasmosis

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From fatal attraction to basic instinct

The 'fatal attraction phenomenon', the switch from rodents' natural fear of the smell of a cat to an attraction to cat smell upon a *Toxoplasma* infection, was described in 2000 (Berdoy *et al.* 2000), and thirteen years after the successful psychological thriller 'Fatal attraction' was produced. Since then, several research groups throughout the world independently confirmed the existence of this phenomenon in about 20 studies performed on mice, rats and even humans. The effect has been shown to be highly specific to the smell of cats, the definitive hosts of *Toxoplasma* (Vyas *et al.* 2007). This behavioural change may be an important part of a manipulation activity of the parasite, by increasing the chance of its successful transmission from the infected intermediate host, for example a rodent, to the definitive host, a cat. Toxoplasmosis-associated behaviour changes, which include prolongation of reaction times and specific changes in personality, are known to increase the probability of traffic and work place accidents in one species of primates (Flegr 2013). It is not known, however, whether similar changes observed in mice and rats also increase the probability of predation accidents in rodents. To date, no predation experiment comparing of prevalence of toxoplasmosis in rodents captured by cats and in a general population of rodents living in the same area has been performed (or at least not published). More research has focused instead on the physiological mechanisms of *Toxoplasma* manipulation activity, producing a wealth of new information in this area. Dopamine has been suspected to play a central role in *Toxoplasma* manipulation for a long time (Flegr *et al.* 2003; Skallová *et al.* 2006). The *Toxoplasma* genome contains two enzymes catalysing the key step in the synthesis of dopamine (Gaskell *et al.* 2009). A large amount of this important neurotransmitter is produced in *Toxoplasma* cysts in the infected host's brain and is exported to surrounding tissue in rodents and likely in humans as well (Prandovszky *et al.* 2011). This increased concentration of dopamine could be responsible for the observed close association between toxoplasmosis and more severe forms of schizophrenia (Holub *et al.* 2013). The second molecule that may be responsible for some behavioural and likely additional morphological differences between infected and noninfected animals, including humans, is the steroid hormone testosterone. *Toxoplasma* upregulates its synthesis by increasing the number of luteinizing hormone receptors on Leydig cells, that is the receptors that regulate the synthesis of testosterone in testes (Lim *et al.* 2013). This explains why *Toxoplasma* increases testosterone level only in men but not women (Flegr *et al.* 2008) and why neither the increase of testosterone, nor associated behavioural changes, exist in castrated male rats (Lim *et al.* 2013).

This study by Shantala A. Hari Dass and Ajai Vyas shows that *Toxoplasma* is a master of all martial arts. It masters both brute force methods (synthesis of dopamine using its own genes) as well as sophisticated methods of modern information war (reprogramming the host's brain by changing regulation of expression of key host genes) to defeat host genes in their invisible but cruel battle for the

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phenotype of the infected host. Contact with the odour of a cat activates medial amygdala circuits responsible for perceiving fear in normal rats. By hypomethylation of certain regulatory elements of a key gene, *Toxoplasma* is able to reprogramme the brain's genetic machinery in such a way that the smell of cat activates, and changes the wiring of, the medial amygdala circuits responsible for sexual behaviour. As another successful movie with Michael Douglas, 'Basic Instinct', clearly shows sexual instincts are stronger than self-protection instincts and not only in male rats. *Toxoplasma*-infected male rats express the 'fatal attraction phenomenon' – they stay longer in places where they smell a cat. Similarly, infected male students rate the smell of diluted cat urine as relatively more pleasant (Flegr *et al*. 2011).

How to change fear to attraction

Using methylation sensitive restriction enzyme digestion in combination with quantitative PCR, the authors of this study show that infected male rats have hypomethylated arginine vasopressin (AVP) promoters in medial amygdala, which leads to higher expression of mRNA for AVP (quantified by cDNA based PCR). This could be the reason for greater activation of the vasopressinergic neurons after exposure to the cat's odour. They also show that the fear of cat smell can be restored by a systemic hypermethylation (by systemic administration of L-methionine) in infected animals. Most importantly, the 'fatal attraction phenomenon' can be induced in noninfected rats by intracerebral delivery of methylation inhibitor into the medial amygdala. Using immunohistochemistry (measuring the number of AVP and Fos colabelling cells in several parts of the brain) and proper controls, authors have shown that cat odour increases the neuronal activation of vasopressinergic neurons in the medial amygdala only in the infected rats.

Parasites and epigenetics

The internal state of a cell or an organism is maintained by a sophisticated, dynamic web of interactions. These interactions are responsible for both the steady-state (feedback) and for ontogenetic trajectories (feedforward). Some functions require continuous 'pressure' of regulating factors (e.g. maintaining the size of gonads during mating season). Other responses lead to more or less stable structures, enduring for the whole life. In this study discussed here, we witness a third possibility – *ad hoc* restructuring of the microanatomy of the amygdala, resulting in behavioural change. The proximate cause of change was induced hormonally, reprogramming cells constituting this anatomical structure by intervention into their chromatin landscape (for exhausting account of such changes, see the ENCODE program, (Gerstein 2012; Ecker 2012; Suzuki & Bird 2008)). Ontogeny is based on such subtle regulations of genetic contexts, and environmental cues can also be 'written down' in this way. Here, the parasite enters the stage as a decisive factor, changing (via hormonal manipulation) the methylation pattern of chromatin in the cells involved. At present, it is a matter of speculation (i) what further changes in chromatin structures are involved and their specificity; (ii) what the changes would be if pups were infected instead of adults; or even (iii) whether such chromatin cues could be transmitted to the next generation (as Dias & Ressler suggest in a different model (2014)). The behaviour of *Toxoplasma*-free children of *Toxoplasma*-infected and *Toxoplasma*-free mothers differs in many aspects (Kaňkova *et al*. 2012), and toxoplasmosis can be sexually transmitted from infected males to females and then to embryos in many species, probably including humans (Flegr *et al*. 2014). It would be interesting to test the behaviour and methylation pattern of sons of infected male rats. Possibly, *Toxoplasma* still has a deposit of surprises prepared for us.

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