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Hot male: can sex in humans be modified by temperature?

John C. McLachlan*, Helen Storey

Peninsula Medical School, Tamar Science Park, Plymouth PL6 8BX, UK

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Abstract

Sex determination in many animals has an environmental component, particularly through temperature. In this article, it is argued that some evidence may by seen for this in humans, and it is proposed that the influence of temperature on sex determination may be a reason for the placing of testicles outside the body cavity in most male mammals.

Keywords: Temperature; Sex; Determination; Human; Testicle

Sex determination by temperature is frequently observed in non-mammalian vertebrates. However, in mammals the SRY gene is believed to initiate a genetic cascade leading to normal male morphology. Some neglected observations can be explained by the hypothesis that genetic sex determination in mammals evolved through co-opting parts of a temperature-dependent mechanism, which may still be expressed under some circumstances. This may be the reason why mammalian testicles are generally found outside the body cavity.

Temperature-dependent sex determination is well known in reptiles, crocodiles, turtles, alligators, fish, and can be demonstrated sparsely in amphibians. It is connected to developmental growth rate (Murray et al., 1990). With sexual dimorphism, differences in morphology must be generated from a common body plan, and temperature can be used to initiate these differences. In a sense, an environmental differential is being employed by the biological system to induce differential gene expression.

It may be assumed that this phenomenon disappeared with the appearance of homoeothermy. However, in evolutionary terms it is unlikely that a major mechanism would vanish in a short time. On the contrary, there are many examples of genetic mechanisms which persist long after their use has disappeared: teeth in avians being perhaps the most striking example.

There are four hard-to-understand observations that may shed light on the relationship between temperature and sex in humans and other mammals.

The first is that males develop a little faster than females from the earliest stages of development, even before the time at which differences in the internal and external genitalia can be identified. Within an individual body, the right side develops a little faster than the left (Mittwoch, 1988). This indicates that the relationship between growth and temperature is not a simple one, since of course both sides are at the same temperature.

The second is the existence of true hermaphroditism in humans. In this very rare condition, one side of the body is male and the other female, although of course the genetic constitution is identical (Mittwoch, 1996). Generally, the male side is the right side, and the female on the left. This indicates that the relationship between sex and genetic constitution is not simple either, since the genetic constitution is the same on each side.

The third is that human males seem to be more common in hot climates (Grech et al., 2000). Of course, this may be a straightforward consequence of a differential viability of male sperm at higher temperatures, but there is no reason to assume that this must be the case, and the direction of the bias is of interest.

The fourth is the strange business of mammalian testicles being placed outside the body cavity. This is achieved during development by the development of a blind sac, the processus vaginalis, which penetrates the musculature of the lower part of the abdominal wall. The testicles leave the body cavity, not through these sacs, but behind the mesodermal wall. The resulting

*Corresponding author. Tel.: +44-01752-764-296; fax: +44-01752-764-226.
E-mail address: john.mclachlan@pms.ac.uk (J.C. McLachlan).

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arrangement is distinctly odd. The weakness can lead to inguinal hernia in later life, and the testicles are placed in a very vulnerable position, as most males become painfully aware on a number of occasions in life. These evolutionary disadvantages are significant: for this morphology to evolve or persist seems to imply that there are overwhelming countervailing advantages. The conventional explanation of this is that sperms are not viable at body temperature and must therefore be kept cooler in order to survive. However, this begs almost all the significant evolutionary questions. Why should sperm not be viable at the conventional body temperature when all other cells in the body are? What happened in evolutionary terms to sperm cells to make them so different, and what happens in developmental terms to male primordial germ cells to make them acquire temperature sensitivity? The cellular mechanisms of temperature sensitivity of sperm in vivo remain unclear. Apoptosis may be involved, and this may be related to oxidative stress, mediated by a heat labile superoxide dismutase (Ahotupa and Huhtaniema, 1992). Sperms have greatly reduced cytoplasm compared to somatic cells, and this may render them less capable of dealing with oxidative stress.

A unifying hypothesis which incorporates all of these pieces of information is that there are rate-determining genes in the genome, not necessarily on sex chromosomes. These *can* be activated by SRY, and when they are, they lead to a faster rate of development (Schmahl et al., 2000), which in turn leads to maleness. These genes can also be activated by temperature. While it has previously been proposed that there are overlapping temperature and genetic mechanisms in mammalian sex determination (Kraak and Pen, 2002) it has been assumed that this activation is a developmental phenomenon, that is, acting solely after fertilization. We propose that rate-determining genes can be activated by temperature during spermatogenesis, and imprinted with this activity. External testicles therefore developed in mammals as a secondary device to ensure that sperms never reached the activation temperature. Subsequent to this, sperms developed temperature susceptibility, which serves to reinforce the phenomenon, in the manner proposed by Newman (1992).

Temperature dependence in humans rarely becomes visible, since it would only occur in the (probably) rather narrow zone between cell death and the activation temperature, and homoeostasis in mammals is reasonably precise. However, in rare circumstances, it could re-emerge.

A prediction of this proposal is that SRY-negative males could occur, if temperature regimes were sufficient to activate the rate-dependent mechanism. Of course, identifying these would only occur if they were sought. Only with a degree of intersex morphology would a genetic analysis be likely. In such cases, human SRY-negative individuals showing male development are indeed observed (Slaney et al., 1998). On occasions, pure bred dogs also show male phenotype without the presence of SRY (Hubler et al., 1999; Meyers-Wallen et al., 1999). SRY-negative hermaphrodites would also be expected, and again this does indeed occur (Koopman et al., 1991). A critical testable prediction would be that sex ratios in mammals could be influenced by temperature effects, without the involvement of differential sperm survival.

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References

Ahotupa, M., Huhtaniema, I., 1992. Impaired detoxification of reactive oxygen and consequent oxidative stress in experimentally cryptorchid rat testis. Biol. Reprod. 46, 1114–1118.

Grech, V., Vassallo-Agius, P., Savona-Ventura, C., 2000. Declining male births with increasing geographical latitude in Europe. J. Epidemiol. Community Health 54, 244–246.

Hubler, M., Hauser, B., Meyers-Wallen, Vn., Arnold, S., 1999. Sry-negative XX true hermaphrodite in a Basset hound. Theriogenology 51, 1391–1403.

Koopman, P., Gubbay, J., Vivian, N., Goodfellow, P., Lovell-Badge, R., 1991. Male development of chromosomally female mouse transgenic for Sry. Nature 351, 117–121.

Kraak, S.B.M., Pen, I., 2002. Sex-determining mechanisms in vertebrates. In: Hardy, I.C.W. (Ed.), Sex Ratios. Cambridge University Press, Cambridge, pp. 158–177.

Meyers-Wallen, Vn., Schlafer, D., Barr, I., Lovell-Badge, R., Keyzner, A., 1999. Sry negative XX sex reversal in purebred dogs. Mol. Reprod. Dev. 53, 266–273.

Mittwoch, U., 1988. The race to be male. New Sci. 22, 38–42.

Mittwoch, U., 1996. Unilateral phenotypic manifestations of bilateral structures: which phenotype matches the genotype? Frontiers Endocrinol. 16, 121–129.

Murray, J.D., Deeming, D.C., Ferguson, M.W., 1990. Size dependent pigmentation-pattern formation in embryos of Alligator mississippiensis: time of initiation of pattern generation mechanism. Proc. R. Soc. London Ser. B 239, 279–293.

Newman, S.A., 1992. Generic physical mechanisms of morphogenesis and pattern formation as determinants in the evolution of multicellular organisation. In: Mittenthal, J., Baskin, A. (Eds.), Principles of Organisation in Organisms, SFI Studies in the Sciences of Complexity. Addison-Wesley, London, pp. 1–27.

Schmahl, J., Eicher, E.M., Washburn, L.L., Capel, B., 2000. Sry induces cell proliferation in the mouse gonad. Development 127, 65–73.

Slaney, S.F., Chalmers, I.J., Affara, N.A., Chitty, L.S., 1998. An autosomal or X-linked mutation results in true hermaphrodites and 46 XX males in the same family. J. Med. Genet. 35, 17–22.