REPRODUCTIVE CONSEQUENCES OF CIRCADIAN DYSFUNCTION: FERTILITY IN THE *BMAL1* NULL MOUSE

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Circadian rhythms are generated by a suite of genes called clock genes that are expressed in the brain and also in many peripheral tissues. In the peripheral tissues, these genes assist in regulating the expression of many genes involved in cell growth, angiogenesis and development. *Bmal1* is a critical gene involved in circadian rhythm generation. Here we report on the fertility and fecundity of *Bmal1* knockout mice (*Bmal1*$^{-/-}$). Male *Bmal1*$^{-/-}$ mice have impaired fertility compared to controls [(litters produced/number of animals) wild type (5/5), CBA controls (5/5), *Bmal1*$^{-/-}$ (1/15)]. Fifty percent of male *Bmal1*$^{-/-}$ mice had defective caudal sperm, showing sperm that was both non-motile and malformed. Seminal vesicle weight was significantly reduced in the *Bmal1*$^{-/-}$ mice (50% reduction) in males at both 4 and 5.5 months old. Female *Bmal1*$^{-/-}$ mice had irregular oestrus cycles and failed to maintain a pregnancy to term following natural mating [(litters produced/number of animals) wild type (5/5) CBA controls (5/5) *Bmal1*$^{-/-}$ (0/5)]. When embryos were flushed from the uterus 4 days after natural mating, there was a reduced number of released oocytes and a reduced development to blastocysts in the *Bmal1*$^{-/-}$ female mice. Following a standard PMSG/HCG super ovulation protocol, *Bmal1*$^{-/-}$ mice showed both a reduction in ovulation rate as well as a slowed progression of embryos to blastocyst stage (Table 1).

Table 1. Embryo development following superovulation of *Bmal1*$^{-/-}$, *Bmal1*$^{+/-}$ and *Bmal1*$^{+/+}$ mice

	Fertile matings (%)	Embryos recovered	Degenerating/unfertilised (%)	2 cell-morula (%)	Blastocyst (%)	Hatching blastocyst (%)
Bmal1$^{+/+}$	50	31 ± 5	9	32	58	1
Bmal1$^{+/-}$	94	33 ± 4	13	36	46	5
Bmal1$^{-/-}$	60	20 ± 5	2	64	31	3

These results suggest that disruption of a key clock gene has detrimental consequences on fertility in the mouse. Further, this reduction in fertility appears to be acting at multiple levels. Continued investigation into the importance of rhythm genes in reproductive function is required.

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