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A genetic mutation has been found that alters the free running period of the locomotor activity rhythm from the wild-type value of =24 hours to =20 hours in homozygous mutants. Our data suggest the existence of two qualitatively different rhythmis outputs from the circadian oscillators contained with the SCN. One of these outputs stimulates the expression of locomotor activity producing "activity rhythms" (which are seen within @'), and the other suppresses the expression of activity, restricting its appearance to a temporally defined window and thereby defining the boundaries of p'. The idea that one function of a circadian output from the SCN is to suppress activity is novel.

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May 4, 1992

Ms. Marilyn J. McKee
Contracting Officer
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A-1

Dear Ms. McKee,

Attached is the Technical Report and Invention Statement for Dr. Michael Menaker's Air Force Grant - Year 2 (Grant # AFOSR-90-0098). Please let me know if additional information is needed.

Thank You.

Sincerely,

Becky L. Abell
Grants Administrator
Biology - UVA

D. Wayne Jennings
Director-Sponsored Programs

AFOSR Report for Year 2

We have continued the study of "temporal chimeras" produced by transplanting SCN tissue from hamsters of one genotype into partially lesioned hosts of a different genotype. A genetic mutation has been found that alters the free running period of the locomotor activity rhythm from the wild-type value of ≈24 hours to ≈20 hours in homozygous mutants. It has been shown previously that a transplant of fetal hypothalamic tissue containing the suprachiasmatic nuclei to a host rendered arrhythmic by a complete lesion of the suprachiasmatic nuclei restores rhythmicity with the free running period which is normally expressed by the donor genotype. We made partial lesions of the suprachiasmatic nuclei of wild-type hosts, which did not completely abolish their circadian rhythmicity, and then placed hypothalamic implants from homozygous mutant fetal donors into the lesion site. Our data suggest the existence of two qualitatively different rhythmic outputs from the circadian oscillators contained within the SCN. One of these outputs stimulates the expression of locomotor activity producing "activity rhythms" (which are seen within $\alpha$'), and the other suppresses the expression of activity, restricting its appearance to a temporally defined window and thereby defining the boundaries of $\rho$'. The idea that one function of a circadian output from the SCN is to suppress activity is novel; as far as we are aware there are no data in the literature that directly suggest this (although many are consistent with it) and it is hard to imagine how such data could be generated without employing some "chimeric" approach such as the one we have reported here. Preliminary results from the histological evaluation of the brains of our temporal chimeras indicate that grafts placed in a number of sites in or

above the third ventricle can result in the successful expression of donor rhythmicity. Therefore, coupling of the circadian output signals to the host's locomotor system appears not to require close proximity between host and donor circadian oscillators. The behavioral aspects of this work are in press in the *Journal of Neuroscience* ("Temporal Chimeras Produced by Hypothalamic Transplants," Michael A. Vogelbaum and Michael Menaker).

We have just completed a study of the brains of 150 transplanted animals to determine which aspects of the transplant procedure influence the expression of host and/or donor rhythmicity. We have examined the effects of lesion size and of the elapsed time between lesioning and implantation (minutes or weeks) on the integration of host and donor circadian inputs by the locomotor output system of the host animal. This work has been prepared for publication and submitted to *Journal of Neural Transplantation and Plasticity* ("Factors Determining Restoration of Circadian Behavior by Hypothalamic Grafts," Michael A. Vogelbaum and Michael Menaker).

Work during the next year will be directed at devising techniques for studying the detailed neuroanatomical connections between graft and host and assessing what if any functional connections are made between the graft and the host's light input system.