BIOGRAPHICAL SKETCH

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NAME: HELLER, H CRAIG

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POSITION TITLE: PROFESSOR OF BIOLOGY AND HUMAN BIOLOGY

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
URSINUS COLLEGE	BS	06/1965	BIOLOGY
YALE UNIVERSITY	MPHIL	06/1968	BIOLOGY
YALE UNIVERSITY	PHD	06/1970	BIOLOGY
SCRIPS INSTITUTION OF OCEANOGRAPHY		01/1972	PHYSIOLOGY

A. Personal Statement

My research has been in the areas of the physiology and neurobiology of temperature regulation, hibernation, sleep, circadian rhythms, and most recently learning and memory and human performance. This diverse set of interests is all inter-related. As a post doc I characterized the mammalian thermostat in hibernators. That work led to the question of whether hibernation was an evolutionary extension of sleep, specifically of NREM (non-Rapid Eye Movement) sleep. What tied these two topics together was our finding that body temperature is regulated at a lower level during NREM sleep, but is not regulated during REM sleep. Subsequent work examined the effect of both ambient and body temperature on sleep in both rodents and humans. Sleep work led to investigating the role of the circadian system in timing sleep and hibernation. Sleep is timed by the circadian system and although the circadian system was damped to enable multiple days of hibernation, activity of the circadian system brought animals out of hibernation for periodic arousals. My lab's EEG studies of hibernation led to the discovery of a huge increase in slow wave activity following each bout of hibernation. That EEG pattern gradually declined to normal levels over about 4 hrs. and its magnitude was a function of brain temperature during the preceding hibernation bout. This finding was at odds with research on sleep homeostasis in non-hibernators. Sleep deprivation leads to an increase in slow wave activity during subsequent sleep, and as in the hibernator, that increase has a monotonic decline reflecting a sleep restorative function. My hypothesis was that this dramatic increase in slow wave activity following hibernation was due to loss of excitatory synapses in the cortex. This investigation led to the remarkable finding that during a bout of hibernation, there was about a 25% loss of dendritic structure and synapses in several brain areas we investigated. The amount of loss was a function of brain temperature during torpor, and the losses were fully restored in the 3 to 4 hrs. following arousal -- a remarkable case of neuroplasticity. Our research on sleep in hibernators continues as we are completing data analysis from a 15 year project in which we recorded EEG, EMG, EKG, and temperatures from 18 bears continuously over 6 months each. Other work in my lab on sleep homeostasis showed the role played by adenosine in the slow wave response following prolonged wakefulness. We also conducted experiments showing that whereas NREM sleep is in a homeostatic relationship with wake, REM sleep is in a homeostatic relationship with NREM sleep. This result produced a new explanation for the NREM/REM sleep cyclicity timing. I have also studied the physiology of human temperature regulation. A main discovery is the importance of the glabrous skin as the major heat loss effector in mammals. This work led to a technology that enhances heat exchange (both directions) through the glabrous skin, which provides the capacity to rapidly rewarm hypothermic individuals such as patients coming from surgery, as well as to rapidly cool hyperthermic individuals like athletes. The latter work led to the discovery that muscle failure is largely due to a rise in muscle temperature, and by extracting heat during

exercise the technology greatly extends endurance, work volume capacity, and conditioning effects. Our recent work has explored the role of sleep and circadian rhythms in learning and memory, and specifically in the learning disability associated with Down syndrome (DS). This work has produced interesting neurophysiological results such as the role of the circadian system in modulating neuroplasticity and the role of NREM sleep in memory consolidation, but the most exciting result has been our demonstration of long-term restoration of learning and memory abilities in mouse models of DS through short-term, chronic treatment with GABA antagonists

B. Positions, Scientific Appointments, and Honors

1972 - 1977 Assistant Professor of Biological Sciences, Stanford University
1977 – 1983 Associate Professor of Biological Sciences, Stanford University
1977 Walter Gores Award for Excellence in Teaching, Stanford University
1983 - present Professor of Biological Sciences, Stanford University
1985 - 1992 Bing Professor of Biological Sciences, Stanford University
1987 - 1988 Chairman, University Committee for undergraduate Studies, Stanford University
1992 – present Lorry Lokey/ Business Wire Professor of Biological Sciences and Human Biology, Stanford
1985 - present Fellow of the AAAS
1992 - 1994 Chair, University Committee on Research, Stanford University
1994 - 1997 Associate Dean of Research, Stanford University
1997 - 2002 Chair, Department of Biological Sciences, Stanford University
2002 - 2010 Chair, Wallenberg Global Learning Network Steering Committee, Stanford University
2009 - Co-Director, Stanford Down Syndrome Center, Stanford University
2010– 2016 Co-Director, Wallenberg Network Initiative on Culture Brain and Learning, Stanford Univers

2000 - 2015 Member, Defense Science Research Council, DARPA
2009 - 2011 Chair, Defense Science Research Council DARPA
2009 – 2011 Chair, APSS Program Committee
2010 Kenneth Cuthbertson Award for Exceptional Contributions to Stanford University
2017 – 2019 Assoc. Editor , Journal of Neurobiology of Sleep and Circadian Rhythms
2018 - present Board of Directors , Sleep Research Society
2019 - present Board of Directors, BSCS (Biological Sciences Curriculum Study)
2020 - 2022 President, Sleep Research Society

C. Contributions to Science

Some of my earliest research was on thermal physiology of mammals and most recently that has focused on humans. We discovered a previously unrecognized mammalian adaptation for heat loss. Although the unusual vascular structures of the non-hairy skin, arteriovenous anastomoses, have been known for a long time, their function was not understood. We showed these structures are the major heat loss effectors of the human body. That work resulted in a number of translational products. Our first studies showed that using these structures in reverse we could eliminate post-anesthetic tremors and speed the recovery of hypothermic individuals. Using the technology for cooling, we showed muscle fatigue is largely due to rise in temperature of the muscle, and if excess heat is extracted, the work capacity of the muscle goes up.

1. Grahn, D., Brock-Utne, J.G., Watenpaugh, D., and Heller, H.C. (1999) Rewarming from mild hypothermia can be accelerated by mechanically distending blood vessels in the hand. J. Applied Physiol. 85(5): 1643-1648
2. Grahn, D.A., Cao, V.H., and Heller, H.C. (2005) Heat Extraction through the palm of one hand improves aerobic exercise endurance in a hot environment. J. App. Physiol 99:972-978
3. Grahn, D.A., Dillon, J.L., Heller, H.C. (2009) Enhancing heat loss through the glabrous skin surfaces of heavily insulated individuals. J. of Biomech. Eng. 131:071005-1-7.
4. Heller, H. C., Grahn, D. A., (2012) Enhancing thermal exchange in humans and practical applications. J. Disrupt. Sci. and Technol. 1(1):11-19.
5. Grahn, D., Makam, M., Heller, H. C. (2018) A method to reduce heat strain while clad in encapsulating outerwear. J. Occupational and Environmental Hygiene. 15(8):573-579.

I am proud of the translational work we have conducted to find a pharmacological treatment for the learning disability of Down syndrome (DS). This project began with a suggestion by a graduate student that the disability could be due to over-inhibition. Pilot experiments with several GABA antagonists supported his hypothesis. We then undertook a major series of pre-clinical experiments on Down Syndrome (DS) model mice examining effects of our drug of choice for going to clinic – pentylenetetrazole (PTZ) – on possible mechanisms responsible for the learning disability including sleep and circadian pathologies as well as developmental and aging processes. Our major results were that a short-term chronic daily treatment with very low doses of PTZ resulted in long-term normalization of learning and memory in the DS mice while having no effect on the 2N controls. The beneficial effects of PTZ were observed at all ages. The treatment had to be delivered during a specific circadian phase and that sleep, following the treatment, was essential for its effect. We also showed that the attention disorder component of DS in these animals was not affected by PTZ treatment, but could be reversed with serotonergic drugs.

1. Munn, G.K. Freeburn. A., Finn, D.P. Heller, H.C. (2022) Hyper-Rigid Phasic Organization of Hippocampal Activity But Normal Spatial Properties of CA1 Place Cells in the Ts65Dn Mouse Model of Down Syndrome. J. Neuroscience 42(8):1542-1556
2. Chuluun B, Pittaras E, Hong H, Fisher N, Colas D, Ruby NF, Heller HC. Suprachiasmatic lesions restore object recognition in down syndrome model mice. Neurobiol Sleep Circadian Rhythms. 2020 May;8:100049. PubMed Central PMCID: PMC7075983.
3. Heller HC, Ruby NF, Rolls A, Makam M, Colas D. Adaptive and pathological inhibition of neuroplasticity associated with circadian rhythms and sleep. Behav Neurosci. 2014 Jun;128(3):273-82. PubMed Central PMCID: PMC4060045.
4. Colas, D., Chuluun, B., Warrier, D. Blank, M., Wetmore, D. Z., Buckmaster, P., Garner, C. C., Heller, H. C. (2013) Short-term treatment with the GABAA antagonist pentylenetetrazole produces a sustained procognitive benefit in a mouse model of Down's syndrome. British Journal of Pharmacology. 169: 76C3-773. PMID: 23489250
5. Heller, HC, Salehi, A, Chuluun, B, Devsmita, DD, Lin, B, Moghadam, S, Garner, C C, Colas, D (2014) Nest building is impaired in the Ts65Dn mouse model of Down syndrome and rescued by blocking 5HT2a receptors. Neurobiology of Learning and Memory. 116:162-171. PMID: 25463650

Our work on DS mice has paralleled work on another rodent model of learning disability that we have developed. When Djungarian hamsters on a 8/16 LD cycle were given an extra 5 hrs. of light on one day, most of the animals became circadian arrhythmic for the rest of their lives. Once arrhythmic, they could no longer perform on short and long term memory tasks. The learning could be restored as in the DS mice with PTZ treatment, and as in the mice, there was a long-term effect of a short-term course of therapy. The PTZ did not restore rhythms. Studying clock gene expression in these animals showed that the clock genes continued to be expressed but not with a circadian rhythm. These results led to the hypothesis that the SCN was actively inhibiting neuroplasticity and fit with our results on the DS animals showing stronger circadian rhythms. Subsequent work showed that lesions of the SCN in the hamsters did not impair their learning and memory even though it rendered them arrhythmic. However, SCN lesions of the arrhythmic hamsters restored their ability to form short and long-term memories. This cumulative work on the hamsters and the DS mice have led to the novel hypothesis that a function of the SCN is to stabilize memory transcripts during the process of memory consolidation that is occurring during sleep. Our other work has shown that memory consolidation requires minimal quanta of continuous NREM sleep and that memories can be altered during the consolidation process.

1. McMartin, L., Kiraly, M., Heller, H.C., Madison, D.V., Ruby, N.F. (2021) Disruption of circadian timing increases synaptic inhibition and reduces cholinergic responsiveness in the dentate gyrus. Hippocampus 31(4):422-434. PMC8048473.
2. Fernandez F, Lu D, Ha P, Costacurta P, Chavez R, Heller HC, Ruby NF. Circadian rhythm. Dysrhythmia in the suprachiasmatic nucleus inhibits memory processing. Science. 2014 Nov 14;346(6211):854-7. PubMed Central PMCID: PMC4459503.
3. Rolls A, Colas D, Adamantidis A, Carter M, Lanre-Amos T, Heller HC, de Lecea L. Optogenetic disruption of sleep continuity impairs memory consolidation. Proc Natl Acad Sci U S A. 2011 Aug 9;108(32):13305-10. PubMed Central PMCID: PMC3156195.

4. Rolls A, Makam M, Kroeger D, Colas D, de Lecea L, Heller HC. Sleep to forget: interference of fear memories during sleep. Mol Psychiatry. 2013 Nov;18(11):1166-70. PubMed Central PMCID: PMC5036945.
5. Ruby NF, Fernandez F, Garrett A, Klima J, Zhang P, Sapolsky R, Heller HC. Spatial memory and long-term object recognition are impaired by circadian arrhythmia and restored by the GABAAAntagonist pentylenetetrazole. PLoS One. 2013;8(8):e72433. PubMed Central PMCID: PMC3756994.

Going farther back our work on various aspects of sleep homeostasis is very significant. We were the first to show that adenosine acting through the adenosine A1 receptor is responsible for the homeostatic intensification of slow wave activity (delta power) during NREM sleep. That result led to our hypothesis that a function of NREM sleep was to replenish brain energy reserves (glycogen) depleted during waking, and that hypothesis stimulated much research in the area of sleep function. We now know that glycogen restoration is not the sole or even the main function of sleep, however, it is still an interesting probable component of sleep homeostasis that is tied into the growing body of information on roles of astrocytes in sleep. Other work on the homeostatic regulation of REM sleep produced evidence that REM sleep is in a homeostatic relationship with NREM. In other words, the expression of NREM sleep creates the need for REM sleep, and the homeostatic expression of NREM sleep requires periodic occurrence of REM sleep. Thus, the NREM/REM cycle is a homeostatic phenomenon and not due to a fixed period oscillator as had been proposed earlier. One very critical consequence of these studies is that they call into question all previous studies involving selective REM sleep deprivation as a means of testing ideas about REM sleep functions. Even a short period of REM deprivation results in interference with the quality of NREM sleep.

Our work on sleep homeostasis in rats led to a number of questions about the intense expression of delta power following bouts of hibernation. We made two interesting discoveries about this phenomenon. First, the delta power following arousal was a function of the brain temperature during the bout and not the length of the bout. Second, sleep deprivation immediately following arousal did not enhance the delta power response, but the response was eliminated. In contrast, sleep deprivation several hours later produced the expected increase in delta power. We hypothesized that the enhanced delta power was the result of loss of excitatory synapses during hibernation and the reduction of delta power reflected the regrowth of those connections. Subsequent work in which we filled cells at different stages of the hibernation and arousal cycle confirmed our hypothesis in a spectacular way. In some brain areas there is a 20 to 25% loss of dendritic structure and a 50% loss of synaptic markers, and it all grows back in 3 to 4 hrs. Also, the magnitude of these losses also reflected the brain temperature during the hibernation bout. Interestingly, even with the massive loss of synaptic markers, there was not a loss of synaptic proteins indicating they were sequestered in a cytoplasmic pool and mobilized during/following the arousal.

1. Benington, J.H., Kodali, S.K., and Heller, H.C. (1995) Stimulation of A1 adensosine receptors mimics the electroencephalographic effects of sleep deprivation. Brain Res. 692:79-85
2. Benington, J. H., Heller, H. C. (1994) REM-sleep timing is controlled homeostatically by accumulation of REM-sleep propensity in non-REM sleep. Am. J. Physiol. 266: R1992-R2000.
3. Larkin, J. E. and Heller, H.C. (1996) Temperature sensitivity of sleep homeostasis during hibernation in the golden-mantled ground squirrel (Spermophilus lateralis). Am. J. Physiol. 270:R777-R784
4. Von der Ohe, C.G., Darian-Smith, C., Garner, C.C., Heller, H.C. (2006) Ubiquitous and temperature-dependent neural plasticity in hibernators. J. Neurosci. 26:10590-10598