CHAPTER 7:

Findings and Discussion

DESCRIPTION OF FINDINGS

C. elegans and its avoidance circuit proved useful for the study of state-specific modulation. We found that almost all genes affecting neuronal activity and excitability had some degree of impact on the sleep phenotypes that were assayed. Therefore, in understanding the regulation of behavior, it was necessary to understand what components of the nervous system were in fact being regulated.

Behavioral evidence suggests that our perception is dramatically dampened during sleep, and that there are physiological changes within individual neurons and their connections to each other.[1] We studied a sensory-motor circuit of *C. elegans* and found that there is long-term dampening at the sensory neuron during lethargus, with allowed dynamic change in the downstream interneurons following previous activation. Furthermore, our data suggest that reversal of sensory dampening is not likely the cause of behavioral reversibility, and it is rather the efficiency of signal transmission from sensory to interneuron that is altered. Changes in dynamics are well correlated with coordinated activity of the command interneurons AVD and AVA. The mechanism for changing signal transmission across the synpase is unclear, and can be due to either transmitter release or activity of the downstream receptors in the interneurons. We also showed that although there is remodeling at the neuromuscular junction during development, there is no suppression of activity downstream of the command interneurons.

Although these studies were not able to pinpoint the modulators that regulate the sleep-like state, we propose that channels and modulators of these channels are likely to be important in the sensory depression exhibited during lethargus. Functional data suggest that these channels are not active in lethargus, and loss of individual channels result in delay of sensory response to channelrhodopsin. It is important to note that these responses are significantly different from their controls, indicating that signal transduction in response to activation occurs.

In addition, we have confirmed adenosine signaling is likely conserved in *C. elegans.* We suggest that the signaling pathways that mediate adenosine signaling are conserved in their function[2]. It would be of interest to see how these mutants affect the deprivation of quiescence during lethargus.

The work in this thesis clarifies how circuit studies can be directly applied to understand behavior and pinpoint components of the *C. elegans* sensory-motor circuit that are important in modulating arousal. Much of the findings in other model organisms have been confirmed, and we have demonstrated how some of these technological methods can be modified for additional

physiological insights and also used for faster more specific screens. The next step is to use them in conjunction with new sequencing technologies and classic genetics to find some amazing new things.

FUTURE DIRECTIONS

Our study of the sensory motor circuits in lethargus is the first to follow processing of sensory information from input stimulus through the sensory neurons and interneurons to its conversion to behavior through the motor neurons. This is a powerful approach that allows characterization of key components of modulation while identifying circuit components do not contribute to changing behavioral dynamics. Our results indicate some intriguing questions regarding the molecular and circuit mechanisms that contribute to sleep behavior. For one, it would be interesting to separate the contribution of molecular drivers that decrease the efficiency of signal transmission at the sensory-interneuron synapses from the effect of long-term sensory neuron inactivity on the excitability of command interneurons. Furthermore, these functional characterizations involving the identity of modified sensory neurons and careful characterization of physiological and behavioral dynamics allow for new hypotheses involving the key molecular regulators involved in sleep-like behavior. We would expect that dampened neurons would be those that express receptors, modulating components, and functional channels in common that allow these neurons to respond to the signals that promote lethargus. Similarly, neurons that are not dampened should not express these genes. Ease of genetics in *C. elegans* allow fast and insightful analysis of these candidates and would better allow us to understand what it means to sleep at the level of the circuit.

REFERENCES

1 Saper, C. B., Scammell, T. E. & Lu, J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* **437**, 1257-1263, doi:nature04284 [pii]10.1038/nature04284 (2005).

2 Porkka-Heiskanen, T. *et al.* Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* **276**, 1265-1268 (1997).