We recently reported evidence implicating fatty-acid binding protein (Fabp) in the control of sleep and memory formation. We used Drosophila melanogaster to examine the relationship between sleep and memory through transgenic overexpression of mouse brain-Fabp, Fabp7, or the Drosophila Fabp homolog, (dFabp). The key findings are that 1) a genetically induced increase in daytime consolidated sleep (naps) correlates with an increase in cognitive performance, and 2) a late “window” of memory consolidation occurs days after the traditionally understood “synaptic” consolidation. Exactly how Fabp-signaling may be involved in converting normal to enhanced long-term memory (LTM) is not known. Here we describe additional data which support relative subcellular compartmental localization of Fabp in regulating stage associations of different forms of memory in Drosophila. Anesthesia resistant memory (ARM) is a longer lasting memory that is produced by massed training, but unlike LTM produced by spaced training, it is insensitive to protein synthesis inhibitors and does not persist as long. We observed that the ratio of ARM to LTM performance index of Fabp7-transgenic flies is proportional to the relative cytoplasmic to nuclear Fabp7 expression level. These data suggest a common lipid-signaling cascade exists between phases of memory formation previously thought to be molecularly distinct.
long-term memory (LTM), which per -
parate phases of long-lasting memory. 10,11
thought to coexist as two unique and dis-
tinct genetic pathways, and therefore are
periods.  ARM and LTM are believed
generated by dispersing 10 training ses-
was sensitive to protein synthesis
is at least one week, differs from ARM
repeated sequentially.10 By comparison,
days with 10 consecutive training sessions
massed training, and can last for multiple
days with 10 consecutive training sessions
repeated sequentially.10 By comparison,
long-term memory (LTM), which per-
sists at least one week, differs from ARM
since it is sensitive to protein synthesis
inhibitors. This longer-lasting memory is
generated by dispersing 10 training ses-
sions with 15 min inter-trial interval rest
periods. ARM and LTM are believed to be
generated independently by dis-
tinct genetic pathways, and therefore are
thought to coexist as two unique and dis-
parate phases of long-lasting memory.10,11
Here, we were interested in deter-
mining whether Fabp7 expression could
also influence the consolidation period
of ARM as it does for LTM. Fabp7-
expressing and wild-type w(isoCJ1) back-
ground flies were trained in the olfactory
conditioning paradigm to elicit ARM
following 10 sessions of massed training
(10XM). Flies maintained at 20°C and
30°C, but not at 25°C, for 4 days following
10XM training elicited a statistically
significant enhancement of ARM com-
pared to w(isoCJ1) (Fig. 1). A comparison
of the amount of Fabp7 protein expres-
sion at each of these three temperatures
shows a differential level of relative
subcellular localization of protein (Fig.
2). Our previous findings suggested
that an increase in Fabp7 nuclear pro-
tein expression (shown again here in
Figure 2) correlated with LTM forma-
tion following training.8 We therefore
compared the relative performance of
ARM to the LTM we previously
described at each of these tempera-
tures in order to determine whether a
relationship exists in these two forms
of memory. The w(isoCJ1) flies show a
progressive increase in the performance
ratio of ARM:LTM with temperature, while Fabp7 expressing flies show an
enhanced ratio of performance at the
temperature extremes (Fig. 3A). We
next compared the relative Fabp7 sub-
cellular localization with this performance
ratio of memory. Plotting the ratio
of ARM:LTM performance against the ratio
of cytoplasmic:nuclear Fabp7 expression
(from Figure 2) revealed a proportionate
correlation of memory and subcellular
localization with temperature (Fig. 3B).
Therefore, increasing the relative level
of Fabp7 between the cytoplasm and the
nucleus during the consolidation period
following training can enhance both
ARM and LTM, respectively. Together,
these data suggest that ARM and LTM
may share some common lipid-mediated
pathways of regulation.
It has previously been shown that
ARM and LTM in Drosophila memory
formation are genetically distinct, since
disruptions of the transcription factors
dCREB2, Adf1, or Notch block LTM
without affecting ARM,12-16 and LTM
remains intact in radish mutants, which
disrupt ARM.13,17 Since these studies pri-
marily focused on disruption of memory
rather than enhancement, the conclusion
that ARM and LTM are genetically dis-
tinct may not be completely unequivocal.
Our evidence presented here suggests that
the relative abundance of a small lipid
transport molecule between the cyto-
plasmic and nuclear compartments can
regulate the formation of different types
of longer-lasting memory after training.
A relative increase in Fabp7 expression in
the cytoplasm during the consolidation
period following massed training pro-
duces ARM enhancement (Fig. 1), while
a relative increase in the nucleus produces
an enhancement in LTM.8 Since Fabp7
flies have reduced sleep at lower tempera-
tures,8 this suggests cytoplasmic lipid-
binding processes may reduce the need
for sleep, which could be beneficial for
the memory enhancement observed dur-
ing ARM consolidation (Fig. 1). Further,
the enhancement in LTM consolidation
generated by an increase in Fabp7 in the
nucleus8 could reflect lipid-signaling in
transcriptional processes important for
sleep and long-term memory (Fig. 4). Our
data suggest that cytoplasmic processes
modulate ARM, while nuclear processes
are important for regulating LTM, and
that lipid-signaling is involved in both
ARM and LTM during the consolidation
period post-training.
Genetic evidence for lipid metabolism
in the regulation of learning impairments
and the homeostatic response to sleep
loss was recently shown.18 Using cDNA
microarrays, changes in gene expres-
sion of another lipid-binding protein,
the Retinoid Fatty-acid binding protein,
Rfagb, have been observed in Drosophila
following ARM and LTM training19 and
following changes in sleep/wake homeo-
statics.20 Whether altering Fabp levels
can regulate changes in sleep induced by
experience-dependent plasticity, cognitive
impairments induced by sleep deprivation,
or the homeostatic response to sleep loss, remain open questions. The identification of specific lipid species involved in the regulation of sleep/wake and during memory consolidation will be important avenues of future research. Our data suggest Fabp signaling is able to modulate memory consolidation in two previously understood to be distinct forms of longer-lasting memory in Drosophila. While our data present the novel finding that a common protein can regulate consolidation of both ARM and LTM, the difference in relative Fabp7 levels in the cytoplasm versus the nucleus still suggest distinct cellular functions, and therefore may not necessarily support the “exclusive memory hypothesis.”10,21 However it is equally unclear whether these Fabp-mediated events coexist, or instead retain independent cellular mechanisms by parallel processes.10 Further determination of the cells and circuits that differentiate ARM and LTM, particularly in the context of Fabp signaling and relative subcellular localization will be required before any conclusions are made on the degree of exclusivity between these two forms of memory. What appears evident is that a role of nuclear Fabp localization may serve as a “gatekeeper” during later consolidation phases of LTM. Thus, discovery of specific lipids bound by Fabps which signal to nuclear orphan receptors, and subsequent changes in transcription of genes during the consolidation period are critical for our understanding of LTM stability. These active areas of research will undoubtedly yield novel targets involved in the cell signaling processes important for neural fitness and overall cognitive health.

Materials and Methods

Transgenic flies, olfactory avoidance conditioning, and protein gel blot analysis were performed with methods and reagents as previously described.8 Anesthesia resistant memory by 10X massed training was performed according to previously published methods.11

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