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Sleep deprivation impairs synaptic tagging in mouse hippocampal slices

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Abstract

Metaplasticity refers to the ability of experience to alter synaptic plasticity, or modulate the strength of neuronal connections. Sleep deprivation has been shown to have a negative impact on synaptic plasticity, but it is unknown whether sleep deprivation also influences processes of metaplasticity. Therefore, we tested whether 5 h of total sleep deprivation (SD) in mice would impair hippocampal synaptic tagging and capture (STC), a form of heterosynaptic metaplasticity in which combining strong stimulation in one synaptic input with weak stimulation at another input allows the weak input to induce long-lasting synaptic strengthening. STC in stratum radiatum of area CA1 occurred normally in control mice, but was impaired following SD. After SD, potentiation at the weakly stimulated synapses decayed back to baseline within 2 h. Thus, sleep deprivation disrupts a prominent form of metaplasticity in which two independent inputs interact to generate long-lasting LTP.

Keywords

Metaplasticity; Synaptic tagging and capture; Hippocampus; Sleep deprivation; Mouse

1. Introduction

The ability to learn and remember, and thereby adapt behavior based on past experience, is critical for survival. These processes are thought to be mediated in large part by synaptic plasticity, in which the strength of particular synaptic links between neurons is modified and then maintained for varying amounts of time in this modified state (Bliss and Collingridge,

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Conflict of interest

The authors declare no competing financial interests.

1993, Hebb, 1949, Martin, Grimwood, & Morris, 2000). Strengthening a synaptic connection is called potentiation, and when this alteration lasts more than a few minutes, it is referred to as long-term potentiation (LTP) (Bliss and Lomo, 1973, Lomo, 2003). LTP can occur in many locations throughout the nervous system, but in rodents it has been studied most thoroughly in the hippocampus (Huang, Nguyen, Abel, & Kandel, 1996, Nicoll, 2017). LTP is typically induced by applying tetanic, or high frequency, trains of stimulation, either once or repeatedly, to a bundle of axons that form synapses onto the neurons of interest. LTP in the CA1 region of the hippocampus has the property of being input-specific, in the sense that applying tetani to a population of neurons via one set of synaptic inputs does not cause non-specific potentiation in other non-tetanized inputs (Andersen, Sundberg, Sveen, & Wigström, 1977).

However, in the last 25 years, it has become increasingly clear that modulation of one set of synapses can in fact influence the ability of other synapses to undergo plasticity. This “plasticity of plasticity” has been termed metaplasticity (Abraham and Tate, 1997). When this phenomenon occurs due to prior activity at the same synapse under-going potentiation, this is called homosynaptic metaplasticity, whereas when prior activity at one synapse can influence the ability for plasticity at other synapses, this is called heterosynaptic metaplasticity (Hulme, Jones, Raymond, Sah, & Abraham, 2014, Young and Nguyen, 2005, Sharma and Sajikumar, 2015). A prominent example of heterosynaptic metaplasticity is synaptic tagging and capture (STC), in which induction of a long-lasting form of plasticity in one set of synapses causes conversion of short-lasting plasticity at another set of synapses into a long-lasting form. This is thought to occur because induction of either short-lasting or long-lasting forms of synaptic plasticity leaves a molecular “tag” at the affected synapses, which allows those synapses to “capture” the plasticity-related proteins created in response to the induction of long-lasting plasticity (Frey and Morris, 1997, Frey and Frey, 2008). This cellular phenomenon was originally described in hippocampal slices (Frey and Morris, 1997), but has also been observed in intact animals (Shires, Da Silva, Hawthorne, Morris, & Martin, 2012), and has potential behavioral correlates, such as the ability to remember otherwise innocuous details better when in the context of a traumatic event (Moncada and Viola, 2007, Reymann and Frey, 2007, Viola, Ballarini, Martínez, & Moncada, 2014). It is clearly important to better understand how an animal’s experiences and environmental and internal conditions influence these processes of metaplasticity.

Sleep deprivation (SD) is one particular condition that affects all too many of us. SD has been shown to impair hippocampus-dependent memory tasks such as contextual fear conditioning, object recognition, and water maze navigation (Graves, Heller, Pack, & Abel, 2003, Guan, Peng, & Fang, 2004, Palchykova, Winsky-Sommerer, Meerlo, Durr, & Tobler, 2006, Peigneux, Laureys, Delbeuck, & Maquet, 2001, Smith and Rose, 1996). In other tasks, such as the Y-maze or 8-box spatial task, performance is more or less maintained in the face of sleep deprivation, but the strategy the animal uses shifts away from a hippocampus-dependent mode (Bjorness, Riley, Tysor, & Poe, 2005, Hagewoud, Havekes, Tiba, et al., 2010b). SD also has a negative effect on synaptic plasticity in the hippocampus (Campbell, Guinan, & Horowitz, 2002, Davis, Harding, & Wright, 2003, Ishikawa et al., 2006, Kim, Mahmoud, Grover, 2005, Kopp, Longordo, Nicholson, & Luthi, 2006, Marks and Wayner, 2005, McDermott et al., 2003, Ravassard et al., 2009, Tartar et al., 2006, Vecsey et al.,

2009). Relevant to the current study, we have shown in mice that a 5-h period of total SD specifically impairs long-lasting forms of LTP that depend on the second messenger cyclic AMP (cAMP) and its target, protein kinase A (PKA) (Vecsey et al., 2009).

Although there have been many studies of the effects of SD on LTP, we are unaware of any published tests of SD on metaplasticity. Therefore, in the current study, we examined the effects of 5 h of total SD on synaptic tagging in mouse hippocampal slices.

2. Materials and methods

2.1. Subjects

All experiments were carried out on young adult (2–3 months old) male C57BL/6J mice from Jackson Laboratories. Mice were individually housed in a temperature-controlled environment on a 12 h/12 h light/dark schedule, with *ad libitum* access to food and water. All experiments were conducted according to National Institutes of Health Guidelines for Animal Care and Use and were approved by the Institutional Animal Care and Use Committee of the University of Pennsylvania.

2.2. Sleep Deprivation

Sleep deprivation was carried out as described previously (Vecsey et al., 2009, Vecsey, Park, Khatib, & Abel, 2015). Briefly, mice were handled for 2–3 min per day for 6 days prior to sleep deprivation. Sleep deprivation was carried out for 5 h beginning at zeitgeber time (ZT) 0–1 by the gentle handling method (Havekes, Vecsey, & Abel, 2012) to achieve nearly complete sleep loss.

2.3. Electrophysiology

Studies of synaptic tagging were carried out by an experimenter blinded to the condition (sleep-deprived or non-sleep-deprived) of the animal. Protocols were based off of previously published work (Huang, McDonough, & Abel, 2006, Park et al., 2014). Mice were killed by cervical dislocation, and hippocampi were rapidly dissected in ice-cold, oxygenated artificial cerebrospinal fluid (aCSF – pH 7.4, containing 124 mM NaCl, 4.4 mM KCl, 1.3 mM $MgSO_4$, 1 mM NaH_2PO_4, 26.2 mM $NaHCO_3$, 2.5 mM $CaCl_2$, and 10 mM D-glucose bubbled with 95% O_2/5% CO_2). Transverse slices (0.4 mm thick) were prepared using a tissue chopper and placed in an interface recording chamber maintained at 30 °C (Fine Science Tools, Foster City, CA). ACSF was constantly perfused over slices at a rate of approximately 1 ml/min. Following a recovery time of at least 1.5 h, field excitatory postsynaptic potentials (fEPSPs) were elicited from Schaffer collateral (area CA3 to area CA1) synapses using bipolar nichrome wire (0.5 mm; AM Systems, Carlsborg, WA) extracellular stimulating electrodes placed in stratum radiatum of CA1. For synaptic tagging experiments, two stimulating electrodes were positioned in such a way as to activate two separate sets of inputs (S1 and S2) onto the same postsynaptic population of neurons (Fig. 1A). Pathway independence was assessed by the absence of paired-pulse facilitation (50 ms interval) between the two pathways. Extracellular fEPSPs in the apical dendrites were recorded using a glass micropipette (1.5 mm OD; AM Systems, Carlsborg, WA) electrode filled with aCSF with a resistance of 2–4 MΩ. Data were acquired using ClampEx 9.2 and a

Digidata1322 A/D converter (Axon Instruments, Union City, CA) at 20 kHz and low pass filtered at 2 kHz with a 4-pole Bessel filter. To examine basal synaptic transmission, input-output curves were generated by measuring the initial slope of the fEPSP in response to systematic increases in the strength of the stimulus. Slices that had maximum amplitude responses of less than 4 mV were rejected. Stimulus strength was set to elicit approximately 40% of the maximum initial fEPSP amplitude. Paired pulse facilitation was then examined at interpulse intervals between 25 and 300 ms. For synaptic tagging longterm potentiation (LTP) experiments, test pulses were delivered to Schaffer collaterals once every minute for 20 min. Slices that did not have stable baseline responses for 20 min were rejected. After 20 min, LTP was induced electrically by using one of two protocols. A massed 4-train protocol (four 1 s, 100 Hz tetanic stimulus trains delivered 5 s apart) was used to induce long-lasting L-LTP in input pathway S1. 30 min later, a 1-train protocol (one 1 s, 100 Hz) in input pathway S2 was used to induce short-lasting S-LTP (see Vecsey et al. (2007): Figs. 1A and 4A/B/C/D, Isiegas et al. (2008): Fig. 3A, Vecsey et al. (2009): Fig. 1D, Bridi et al. (2013): Fig. 4A/B, and Bridi, Hawk, Chatterjee, Safe, and Abel (2017): Figs. 3A and A) for examples de-monstrating the decremental nature of this form of LTP in isolation). After induction of synaptic potentiation in S2, test pulses were delivered once per minute for two hours to assess the efficacy of the synaptic tagging and capture process.

2.4. Statistics

We performed a mixed-model ANOVA using Sleep Condition (SD vs. NSD) as a between-subject factor, and Time Point (average of first 20 min vs. average of last 20 min) and Input Pathway (S1 vs. S2) as within-subject factors. When significant overall effects and interactions were found, Student's *post hoc* tests were used to look for specific differences. JMP11 was used for all statistical analysis.

3. Results

In our synaptic tagging protocol, we chose to use massed 4-train 100 Hz LTP as our strong stimulus because this stimulation protocol induces a long-lasting form of plasticity that engages synaptic tagging mechanisms (Park et al., 2014) and that is itself resistant to the effects of sleep deprivation (SD) (Vecsey et al., 2009). We chose 1-train 100 Hz LTP as our weak stimulus because synapses experiencing that form of stimulation can be enhanced through synaptic tagging and capture (Huang et al., 2006, Park et al., 2014), and because 1-train LTP is unaffected by SD (Vecsey et al., 2009). By choosing these two SD-independent protocols, we hoped to observe whether the synaptic tagging process, in which a weak stimulus is enhanced by pairing it with a strong stimulus, was susceptible to disruption by SD.

In non-sleep-deprived (NSD) animals, tagging occurred effectively between massed 4-train through pathway S1 and 1-train through pathway S2 – both pathways experienced sustained potentiation (Fig. 1B and C). On the other hand, in SD animals, tagging was blocked – although plasticity induced by massed 4-train was long lasting, the paired 1-train stimulation returned to baseline (Fig. 1D and E). Statistical analysis found that there was an overall interaction between sleep deprivation, input pathway, and time point ($F(1, 24) = 4.01$, $p =$

0.05). Post-hoc analysis found that, during the first 20 min following tetanization, SD did not have a significant effect on either pathway S1 or S2. However, during the last 20 min of the recording, SD significantly reduced synaptic strength in the S2 pathway, but did not affect the S1 pathway.

4. Discussion

We originally hypothesized that a short period of total sleep deprivation (SD) would affect the synaptic tagging and capture (STC) form of heterosynaptic metaplasticity in the mouse hippocampus. The results supported this hypothesis – homosynaptic massed 4-train LTP and 1-train LTP were normal in SD mice, as had previously been demonstrated (Vecsey et al., 2009), but the STC process when these two stimulus protocols were applied 30 min apart was strongly impaired. These results demonstrate that SD can negatively affect the capacity for metaplasticity between inputs. Thus, in SD animals, plasticity induced in one set of synapses in the hippocampus may have an altered ability to influence the flexibility of other synapses in the same neurons, which could have widespread behavioral significance.

A major question resulting from this finding is which molecular and cellular mechanisms underlie this effect, and future experiments will be required to explore this issue. Synaptic tagging has previously been shown to rely on cAMP and PKA (Young, Isiegas, Abel, & Nguyen, 2006), and SD clearly negatively regulates cAMP signaling (Vecsey et al., 2009, Havekes et al., 2014). Thus, this molecular pathway may be the relevant target of SD that blocks the STC processes. SD also causes widespread misregulation of protein synthesis (Vecsey et al., 2012, Tudor et al., 2016), and may cause insufficient and/or incorrect products to be produced that would be needed for either tag or capture mechanisms. Assuming that strongly stimulated synapses are more likely to capture PRPs than are weakly stimulated synapses, if SD reduces the overall pool of PRPs, strongly stimulated synapses may still be able to capture enough PRPs to undergo stable potentiation, whereas weakly stimulated will not. This could explain why synapses receiving strong stimulation had stable long-lasting LTP even in SD conditions, whereas capture of PRPs at weakly stimulated synapses was impaired.

A variant of this idea is that the products are made normally, but are not localized correctly to the appropriate synapses. This could be true of the “tag” molecules, which should normally be maintained for at least 60 min at the weakly and strongly stimulated synapses, or the plasticity-related products (PRPs), which should only be produced robustly in response to strong stimulation (Frey and Morris, 1997, Frey and Morris, 1998). There appears to be control over the subcellular localization of the PRPs. For example, in hippocampal area CA1, cross-tagging between apical and basal dendritic compartments is absent or at least has a higher threshold for synaptic tagging and capture (Alarcon, Barco, & Kandel, 2006, Sajikumar, Navakkode, & Frey, 2007). Placing and maintaining a synaptic tag are also dependent on precise localization of cAMP/PKA signaling via A Kinase Anchoring Proteins (AKAPs) (Huang et al., 2006, Young et al., 2006), which are known to interact with PKA itself as well as other components of the cAMP pathway, such as adenylate cyclases and phosphodiesterases (Colledge and Scott, 1999). Interestingly, AKAP150 protein is downregulated in the mouse hippocampus following 6–12 h of total SD (Hagewoud,

Havekes, Novati, et al., 2010a). If SD were capable of disrupting these processes of localization, PRPs might be distributed throughout the post-synaptic neuron and thus diluted to a point where they would not be adequately captured, and/or PRPs might simply not be captured by the poorly localized tags.

However, it is important to note that we found that synapses stimulated with strong massed 4-train are still capable of capturing PRPs and maintaining stable potentiation normally. Thus, PRPs do in fact appear to be made correctly and distributed normally, at least to the strongly stimulated synapses. This argues against some of the explanations we have laid out in the previous paragraphs. We therefore believe that the most likely explanation for SD's ability to impair STC is that SD disrupts the process of placing a long-lived tag at weakly potentiated synapses. It is currently unknown why tags set by 1 tetanus are disrupted by SD but tags set by 4 tetani spaced 5 s apart are unaffected by SD. As touched on above, a possible explanation is that the 5-h period of SD used in this study has been shown to impair cAMP/PKA signaling via an increase in phosphodiesterase PDE4A5 activity (Vecsey et al., 2009). Tag setting by 1 tetanus in a very similar protocol to our own was shown to be dependent on PKA, whereas tag setting during massed 4-train LTP was shown to be PKA-independent (Young et al., 2006), confirming other findings (Kim, Huang, Abel, & Blackwell, 2010, Woo, Duffy, Abel, & Nguyen, 2003). Thus, brief SD and disruption of cAMP/PKA have very similar patterns of effects on these forms of synaptic plasticity and metaplasticity, suggesting that cAMP/PKA blockade may mediate the effects of SD on synaptic tagging.

In the current study, we applied the strong massed 4-train stimulation first, followed 30 min later by weak 1-train stimulation to the second input. In future studies, this order could be reversed, which would allow us to alter the delay between weak and strong stimuli in order to determine if the tag at weak synapses decays faster in SD animals than in controls (Frey and Morris, 1998). It will also be of interest to test if SD alters additional forms of metaplasticity. For example, in this study we examined STC between two forms of synaptic potentiation. However, synapses given prolonged low-frequency stimulation undergo long-term depression (LTD), and strong LTD and weak LTD protocols can engage in STC as well, and "cross-tagging" can even occur between LTD and LTP (Sajikumar and Frey, 2004). For example, pairing a strong LTP protocol through one input pathway with a weak LTD protocol through a second input pathway results in enhanced longevity of the synaptic weakening at the synapses receiving the LTD stimulus. The mechanisms for these forms of cross-tagging appear to be different, depending on whether LTP is capturing LTD or vice versa (Sajikumar et al., 2007). For example, calmodulin-dependent kinase II (CaMKII) is required to set the tag at synapses undergoing weak LTP, such that those synapses cannot capture PRPs produced by either strong LTP or strong LTD through independent inputs. However, extracellular signal-related kinase (ERK) is not required for those actions, but IS required to set the tag at synapses undergoing weak LTD (Sajikumar et al., 2007). Thus, future study could examine whether SD selectively impairs STC processes associated with LTP or whether metaplasticity involving LTD is also affected, and the results could provide insight as to the relevant molecular mechanisms targeted by SD.

The synaptic homeostasis hypothesis (Tononi and Cirelli, 2014) posits that during wakefulness there is a net increase in synaptic strength due to daily learning. Sleep then allows for restitution of the overall set point for synaptic weight by non-specifically downscaling the strength of all synapses. We highlight two recent reports that are supportive of this concept. The first found that structural down-regulation of synapses occurs in the motor cortex during sleep as compared with wake (de Vivo et al., 2017). The second broadly examined mouse forebrain tissue and found widespread sleep-associated reductions in the synaptic levels of GluA1 and GluA2 AMPA-type receptors, which are strong determinants of glutamatergic synaptic strength (Diering et al., 2017). However, in our studies focused on the hippocampus, SD does not appear to cause widespread synaptic strengthening, as baseline synaptic strength is unchanged between animals receiving 5–6 h of total SD and undisturbed, sleeping controls (Vecsey et al., 2009, Florian, Vecsey, Halassa, Haydon, & Abel, 2011). In fact, 5 h of SD may have the opposite effect, predisposing hippocampal synapses to weaken. Havekes et al. (2016) recently reported that SD decreases CA1 dendritic length and spine density, via a cell signaling pathway mediated by increased activity of cofilin, a F-actin severing protein. We found here that SD prevented time-limited metaplasticity between synaptic inputs onto the same neurons. These findings highlight the fact that SD can have much more targeted effects on synaptic plasticity than proposed by the synaptic homeostasis hypothesis.

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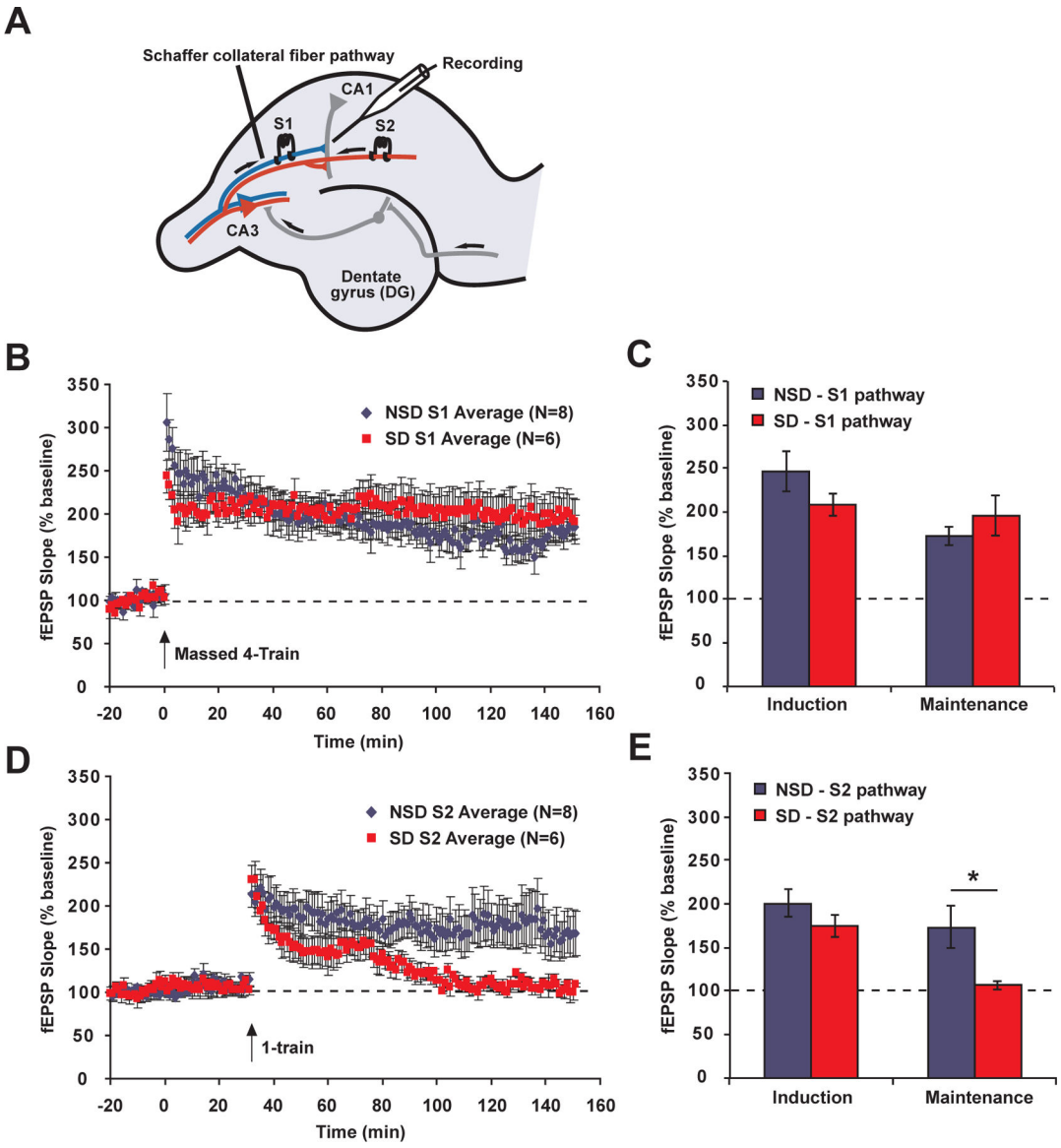

Fig. 1.

Sleep deprivation impairs synaptic tagging. C57BL/6J mice were deprived of sleep for 5 h by gentle handling (SD) or were left undisturbed in their home cages (NSD). *In vitro* field recordings were made in hippocampal slices taken immediately following the deprivation period. (A) Two stimulating electrodes were positioned along the Schaffer collateral fiber pathways in such a way as to activate two separate sets of stimulus inputs (S1 and S2) onto the same postsynaptic population of neurons in CA1. (B and C) In S1, at 0 min, strong stimulation of the massed 4-train type (four 1 s, 100 Hz trains of electrical stimuli with a 5-s inter-train interval) produced normal long-lasting potentiation in NSD and SD mice. (D and E) In S2, at 30 min, weak stimulation (one 1 s, 100 Hz train) in NSD mice resulted in long-lasting potentiation, and this synaptic tagging and capture process was impaired in SD mice. Arrows indicate timing of tetanic stimulation. Error bars indicate SEM. * indicates a post hoc test with $p > 0.05$.