Research

Hormonal and monoamine signaling during reinforcement of hippocampal long-term potentiation and memory retrieval

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Recently it was shown that holeboard training can reinforce, i.e., transform early-LTP into late-LTP in the dentate gyrus during the initial formation of a long-term spatial reference memory in rats. The consolidation of LTP as well as of the reference memory was dependent on protein synthesis. We have now investigated the transmitter systems involved in this reinforcement and found that LTP-consolidation and memory retrieval were dependent on β -adrenergic, dopaminergic, and mineralocorticoid receptor (MR) activation, whereas glucocorticoid receptors (GRs) were not involved. Blockade of the β -adrenergic signaling pathway significantly increased the number of reference memory errors compared with MR and dopamine receptor inhibition. In addition, β -adrenergic blockade impaired the working memory. Therefore, we suggest that β -adrenergic receptor activation is the main signaling system required for the retrieval of spatial memory. In addition, other modulatory interactions such as dopaminergic as well as MR systems are involved. This result points to specific roles of different modulatory systems during the retrieval of specific components of spatial memory. The data provide evidence for similar integrative interactions between different signaling systems during cellular memory processes.

Reinforcement of hippocampal long-term potentiation (LTP) in the dentate gyrus (DG)—i.e., the protein synthesis-dependent transformation of an early-LTP (which can last up to ~5–6 h) into a late-LTP (with a duration of at least 24 h) by behavioral stimulation—has been shown for water reward (Bergado et al. 2003), novelty detection under moderate stress (Straube et al. 2003; Kemp and Manahan-Vaughan 2004), and novelty perception under high acute stress (Korz and Frey 2003, 2005). Reinforcement is assumed to underlie “tagging”-like processes: A weak glutamatergic input sets a “synaptic tag” that captures and processes plasticity-related proteins (PRPs), the synthesis of which is induced by a temporally related heterosynaptic afferent input (Frey and Morris 1997; Korz and Frey 2004; Reymann and Frey 2007). Reinforcement of DG-LTP by novelty detection during moderate stress depends on β -adrenergic activation (Seidenbecher et al. 1997), which is not required during high acute stress conditions (Korz and Frey 2005) but is dependent on hormonal signaling by activation of corticosterone binding mineralocorticoid receptors (MRs).

The establishment of a long-lasting spatial memory has also been reported to depend on β -adrenergic activation (Sara 1985; Decker et al. 1990; Cahill et al. 2000). In addition, the activation of dopaminergic D1 receptors modulates memory in a spatial reference memory task (Liao et al. 2002). Moreover, also MR are involved in spatial reference learning (Smythe et al. 1997b; Yau et al. 1999). The requirement of these different signaling systems for memory formation has been related to different aspects of the complex learning task: β -adrenergic signaling to attention (Sara et al. 1994), dopaminergic activation to reward (Rossetti and Carboni 2005), activated MR to food deprivation (Douma et al. 1998), or anxiety-like behavior (Smythe et al. 1997a). The different activations are located in different brain areas, which therefore have to communicate during spatial learning. However, in-

tegrative studies in combining these effects within one task are still missing.

The present study aimed at the identification of possible interactions between these signaling systems during spatial learning by using a holeboard training protocol that has been shown to result in a reinforcement of LTP (Uzakov et al. 2005). Furthermore, the parallel acquisition of data on the cellular and behavioral level should allow the comparison of possible integrative interactions and their outcomes on both levels.

Results

There was no difference between control groups (combined group for the glucocorticoid receptor [GR] and MR controls) in latencies ($F_{(2,23)} = 0.63$, $P > 0.1$), in reference errors ($F_{(2,23)} = 1.61$, $P > 0.1$) and in working errors ($F_{(2,23)} = 1.48$, $P > 0.1$). According to these findings, during further analyses the different control groups were combined to one sample and compared to the experimental groups (the separated comparisons of the experimental groups with their time matched controls are presented in the supplemental material). In Figure 1 the latencies to find all pellets and the numbers of reference and working errors over the first nine trials are presented. All groups showed a substantial improvement in behavioral performance during the standard training session on day 2, and no differences between groups could be noted.

The maintenance of LTP differed significantly between groups ($F_{(7,59)} = 11.87$, $P < 0.001$). Animals treated with the β -adrenorenergic receptor antagonist ($P < 0.001$; Fig. 2A), dopamine receptor antagonist ($P = 0.001$; Fig. 2B), and MR-antagonist ($P = 0.008$; Fig. 2D) showed a depotentiation after the last trial and significantly impaired LTP compared with their respective control groups, whereas GR-antagonist-treated animals (Fig. 2C) showed no difference compared with controls ($P > 0.1$). Similar as in behavioral performance, no significant difference in LTP between the control groups could be noted ($P > 0.1$ each).

The comparison between the experimental animals and the combined control sample (see Fig. 4E) revealed an overall signifi-

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Figure 1. Similar learning curves of all groups prior to treatment. Latencies to find all pellets (A), number of reference errors (B), and working memory errors (C) for control ($n = 24$) and animals treated with a β -adrenergic antagonist (Beta-ad-ant; $n = 8$), a dopamine D1/D5-receptor antagonist (D1/D5-ant, $n = 10$), a GR-antagonist (GR-ant, $n = 7$), or a MR-antagonist (MR-ant; $n = 10$) for the first nine trials. Given are the means and SEM. The inserted drawing represents the pattern of baited holes (filled circles) and nonbaited holes (open circles) and the start position of the holeboard task.

cant difference in LTP between groups ($F_{(4,54)} = 15.29$, $P < 0.001$). Similar as for the analysis with separate control groups, the pairwise comparisons resulted in significant differences between animals treated with a dopaminergic ($P < 0.001$), a β -adrenergic ($P < 0.001$), and a MR ($P < 0.001$) antagonist but not between GR-antagonist-treated animals ($P > 0.1$) and controls.

During trial 9, i.e., in the absence of antagonists, we found no differences in behavioral parameters between the different groups (latency: $F_{(4,54)} = 0.68$, $P > 0.1$; reference memory error: $F_{(4,54)} = 0.89$, $P > 0.1$; working memory error: $F_{(4,54)} = 1.09$, $P > 0.1$; Fig. 3A), whereas in presence of the antagonists during trial 10 experimental and control animals differed significantly in latencies ($F_{(4,54)} = 8.34$, $P < 0.001$), in reference memory errors ($F_{(4,54)} = 11.81$, $P < 0.001$), and in working memory errors ($F_{(4,54)} = 4.45$, $P = 0.004$; Fig. 3B). By post-hoc tests, we noted significantly elevated latencies in all experimental groups ($P < 0.05$ each) except in the GR-antagonist-treated group. In addition, all former groups made more reference memory errors than did controls ($P < 0.05$), but only the animals treated with propranolol showed more working memory errors ($P = 0.002$). Thus, the most pronounced effect on behavior could be elicited by application of the β -adrenergic antagonist. This becomes even more apparent by comparing the intragroup difference in behavioral performance between trials 9 and 10 (Fig. 3C). We found significant differences between groups in latencies ($F_{(4,54)} = 4.07$, $P = 0.006$) and reference memory errors ($F_{(4,54)} = 6.52$, $P < 0.001$; Fig. 3B) and a tendency toward a difference in working memory errors, although not yet statistically significantly different ($F_{(4,54)} = 2.34$, $P = 0.066$). The post-hoc test revealed significantly longer latencies in animals treated with propranolol ($P = 0.013$) or the MR-antagonist ($P = 0.10$) compared with controls, whereas only propranolol-treated animals showed a significant difference to controls in reference ($P < 0.001$) and in working memory errors ($P = 0.017$).

These results indicate that the behavioral differences between control and experimental animals cannot be related to

reduced general activity of drug-treated rats, because making more errors requires higher locomotor activity. Second, the differences were not related to nonspatial learning strategies. A nonspatial strategy could be represented by a behavior that could be described as just to run along the line of baited holes instead of orienting toward external cues. However, we found no differences between groups in the maximal number of pellets eaten in a row ($F_{(4,54)} = 0.39$, $P > 0.1$; Fig. 4A). Further, a typical searching strategy during the learning trials consisted of poking the head randomly into holes, which includes revisiting of the same holes. This behavior declined with increasing learning success, with no differences between groups (Fig. 4B). This behavior was reactivated during the last trial in some of the drug-treated groups, resulting in a significant difference between groups ($F_{(4,54)} = 7.20$, $P < 0.001$) with higher numbers of revisits in dopamine ($P = 0.017$) and β -adrenergic ($P < 0.001$) receptor antagonist-treated animals, whereas GR ($P = 1.0$) and MR ($P = 0.075$) antagonist-treated animals showed no difference compared with controls (Fig. 4C). Thus, the drugs

did not induce unspecific behavioral alterations but set the animals back to a level of behavioral performance that was typical for initial learning trials.

Finally, a difference in overall learning abilities between groups could not contribute to the differences in performance during the last trial, because we found no differences in latencies or working memory errors before drug treatment between the different groups (Fig. 1A–C).

Discussion

Our results revealed similar processes of memory retrieval at two different organizational levels: at the cellular and at systemic, behavioral level. Cellular as well as system's memory recall required a complex interplay between different signaling systems, i.e., between monoamine (dopamine, noradrenaline) and hormonal (corticosterone) signaling. The more detailed analyses revealed that the differences in behavior were not related to an altered locomotor activity or to different behavioral strategies of substance-treated animals. Additionally, during former studies it has been shown that the drugs at the concentrations used here have no effects on baseline transmission or LTP per se (Pavlidis et al. 1995; Frey et al. 2001; Korz and Frey 2003; Straube et al. 2003).

The role of β -adrenergic and dopaminergic activation in memory recall and LTP-reinforcement

It is well established that β -adrenergic activation is involved in the consolidation and retrieval of contextual fear memories (Cohen and Hamburg 1975) and spatial memories that were driven by emotional and nonemotional processes (Sara 1985; Decker et al. 1990; Przybylski et al. 1999; Cahill et al. 2000; Liao et al. 2002). Furthermore, activation of dopaminergic D1 receptors has been reported to be required for memory consolidation in a spatial reference memory task (Liao et al. 2002), when dopamine function was blocked within the medial prefrontal cortex (PFC) (Levin 1988; Seamans et al. 1998; Kozlov et al. 2001; DeOliveira

Figure 2. Dopaminergic and β -adrenergic receptor blockade as well as inhibition of MR prevents LTP-reinforcement. LTP of animals treated with a β -adrenergic-antagonist (A), a dopamine D1/D5-receptor antagonist (B), a GR-antagonist (C), or a MR-antagonist (D), and the respective controls. In E the controls were combined ($n = 24$) and compared with the treated animals. Given are the means and SEM. (F) The insets show analog traces of evoked potentials of representative substance-treated individual animals at baseline recording, at the 3-h and 24-h time points. Abbreviations as in Fig. 1.

and Nakamura-Palacios 2003), the nucleus accumbens (Ferretti et al. 2005), or the septum (Simon et al. 1986).

For the retrieval of the long-lasting reference memory as well as for the formation of the transient working memory, the major required signaling input is of a β -adrenergic nature. However, we suggest that the β -adrenergic mechanisms that underlie these two kinds of memories are not identical. The working memory depends on a sufficient level of attention (Sara et al. 1994) that is modulated by β -adrenergic activation within the PFC (Rossetti and Carboni 2005), and allows the trial-specific, selective attention to discriminate between already visited or nonvisited baited holes. Elevated levels of noradrenaline within the PFC were found only in T-maze-trained animals compared with only food-rewarded animals, indicating a role of noradrenaline in spatial goal-directed behavior (Rossetti and Carboni 2005), which is most likely triggered by the activation of the locus coeruleus (LC), the main source of noradrenaline within the brain. The LC is mutually connected with the PFC (Vives et al. 1983; Arnsten and Goldman-Rakic 1984; Bouret and Sara 2004; Devoto et al. 2005) and in turn projects into the DG (Harley 1991). Therefore, additional modulation of the β -adrenergic system can be provided by dopaminergic processes. Since there are no reports of the existence of D1/D5 receptors within the DG,

the dopaminergic effect must be indirect, most likely related to processes within the PFC. The PFC is known to be involved in reward (Rossetti and Carboni 2005) and stress sensitive tasks. The latter is characterized by releasing high levels of dopamine and noradrenaline in response to stress (Marsteller et al. 2002; Stalnaker and Berridge 2003). The reward, however, is not the food intake but the execution of the correct spatial behavior. This is indicated by animals that received food without spatial learning in the holeboard and that did not show LTP-reinforcement (Uzakov et al. 2005). There is also a mutual communication between the basolateral amygdala (BLA), which is involved in the processing of emotionally arousing information, and the PFC (Roosendaal et al. 2004a) as well as the hippocampus (Roosendaal et al. 2004b), which are both mediated by noradrenaline and probably depend on MR signaling as well (Korz and Frey 2005).

Corticosteroid receptor activation: Modulation of β -adrenergic activity?

Smriga et al. (1998) found the MR-mediated enhancement of synaptic plasticity in the DG *in vivo* depends on β -adrenergic activity. Recently it has been shown in renal cells that activated MR can interact with β -adrenergic receptors, resulting in enhanced cAMP signaling (Christ et al. 2005) that may activate protein synthesis. Therefore, it is possible that attention modulated by β -adrenergic activity is generally increased or more goal-directed to the food collecting task by the MR effects that on its part may be related to food deprivation

(Douma et al. 1998). We found chronically elevated concentrations of corticosterone due to the food deprivation (Uzakov et al. 2005) that also have effects on receptor densities and affinities (Meyer et al. 2001; Sebaai et al. 2001; Karandrea et al. 2002; Hugin-Flores et al. 2004; Shors 2004). However, we also measured a significant transient increase in response to the holeboard transfer irrespective of the amount of trials the animals experienced, so we cannot rule out that the MR effects are partly related to anxiety (Smythe et al. 1997a).

There is a small number of reports that note an involvement of MR during spatial reference learning (Smythe et al. 1997b; Yau et al. 1999) that interestingly seems to be restricted to young adult animals (8 mo) compared with senile animals (Yau et al. 1995). Oitzl and DeKloet (1992) found different aspects of spatial orientation being affected by MR or GR blockade. Whereas the first resulted in altered search-escape strategies, the second led to increased latencies to find the platform in the water maze. These MR effects and that of Smythe et al. (1997b) are interpreted that MR-blockade results in a selective reduction of the animal's reactivity to extraneous stimuli fit with our hypothesis that the attention to environmental stimuli may be altered by the MR-blockade through β -adrenergic mechanisms. Whereas Oitzl and DeKloet (1992) report increased latencies to find the platform in

Figure 3. The blockade of β -adrenergic receptors has the most pronounced effect on behavioral performance as compared with controls. Latencies to find all pellets (left panel) and numbers of reference and working memory errors (right panel) of treated animals and combined controls during trial 9 (A), trial 10 (B), and the difference in behavioral performance between trial 9 and 10 (C). Given are the means and SEM. Abbreviations as in Fig. 1.

a water maze task by GR-blockade after training, Roozendaal et al. (2004b) found an impairment of spatial memory retrieval in the water maze by the application of a specific GR-agonist that, similar to the enhancement of memory consolidation by corticosterone (McIntyre et al. 2003), depends on noradrenergic activity within the BLA. These results and the lack of a GR-effect in our holeboard task, which elicits only mild stress, point to task-dependent differences in activations of different brain regions and the corticosterone as well as β -adrenergic-mediated mechanism within these regions. In addition, we recently were able to show that acute stress rapidly up-regulates MR but not GR within the DG (Ahmed et al. 2006). Thus, MR signaling can be modulated not only on the hormonal but also on the receptor level, counterbalancing the saturation of MR, even during basal corticosterone levels, due to their higher affinity. This influences the relative occupancy of the steroid receptors, which is crucial for glucocorticoid effects on memory and LTP (Roozendaal 2002).

Systemic and cellular memory recall:

A complex interplay

Recently it has been shown that recall of memories 6 h and 24 h after consolidation requires protein synthesis (Kemenes et al.

2006), suggesting that processes activated during training persist beyond time windows classically described for consolidation (Fulton 2006). Similar mechanisms can explain our results, that synthesis of PRPs during recall induce reinforcement of LTP by tagging-like processes. This is related to the recall of the long-lasting reference memory because the transient working memory cannot be influenced by protein synthesis inhibitors (Uzakov et al. 2005). However, we cannot fully exclude that the applied drugs may have effects on processes not directly related to memory formation. If β -adrenergic and also MR blockade would influence attention as described above, this could also nonspecifically affect the behavioral performance and subsequently LTP-reinforcement by the absence of PRPs, which synthesis is normally induced by the recall. A similar effect can be induced by the application of the dopamine receptor antagonist, in this case related to altered motivations, e.g., to search for the food pellets. The specific effects of the different drug treatments and possible causal relationships between the behavioral performance and LTP reinforcement have to be revealed during further studies.

However, a first scenario can be outlined as follows: The cellular modulation within the DG is, in contrast to the behavioral level, an "all or none"-response (cf. O'Connor et al. 2005); i.e., the blockade of one of the signals leads not only to no rein-

Figure 4. No difference between groups in behavior indicating non-spatial strategies and locomotor activity. Maximum number of pellets eaten in a row (A), number of revisited holes during the first nine trials (B) and during trial 10 (C) for treated animals and combined controls. Given are the means and SEM. Abbreviations as in Fig. 1.

forcement but to an impairment of LTP. The impairment of LTP is very likely related to the lack of perception of novel information during post-tetanic behavioral manipulation. A similar depotentiation of LTP as observed here can be induced by just handling the animals in a familiar context (Korz and Frey 2003), pseudotraining, or repetitive supply of food reward without spatial information (Uzakov et al. 2005), therefore, experiences that do not provide relevant new information. The reinforcement of LTP, in contrast, seems to be related to the perception of novel or the processing of task-related reinforcing information. Thus, depotentiation may protect the hippocampus from an overload of irrelevant information, whereas reinforcement supports the storage of relevant information.

How can the apparent discrepancy between the cellular and the behavioral level be explained? Complex spatial tasks depend on hippocampal activity, but the hippocampus is not exclusively involved in the formation of spatial memories. Different information components, such as contextual, emotional, reward, and temporal aspects, that are processed in different brain areas requiring specific transmitter signaling, e.g., within the PFC, the amygdala, the LC, in which LTP-reinforcement-like processes may take place, establish a multistructural functional network, resulting in the adequate cellular response within the hippocampus (Korz and Frey 2004). These components are necessary but not sufficient for a full memory recall or LTP consolidation. The missing of one of the components impairs the cellular response and the memory recall as indicated by behavioral performance. Even if one receptor subtype (e.g., D1/D5 receptors) would be blocked throughout the entire brain—due to the i.c.v. application of drugs—brain regions involved in memory recall requiring β -adrenergic activation would be still active and serve their function, which is recognized by the behavioral performance. However, it remains to be identified whether, and which, extrahippocampal brain regions are specifically involved and if their activity would be causally related to the observed modulation of hippocampal LTP.

Materials and methods

All experiments were carried out according to the national animal care guidelines and with permission of the regional council of Saxony-Anhalt. Male Wistar rats (8 wk old) from the breeding colony of the institute were kept under a 12 h:12 h light regimen with lights on at 6:00 am in standard cages (40 cm $\times$ 25 cm $\times$ 18 cm), with the ground covered with commercial bedding material (ssniff, wood spans). The animals were fed with food pellets (Ssniff, R/M-H) and tap water was given ad libitum.

Surgery and electrophysiological recording

Rats were anaesthetized with Nembutal (40 mg/kg, i.p.). A monopolar recording electrode (insulated stainless steel, 125 μ m in diameter) was stereotactically implanted into the hilus (coordinates: AP -2.8 , L 1.8 from bregma, 3.2 – 3.5 ventral from dura) of the DG of the right hippocampus, a bipolar stimulation electrode into the medial perforant path (coordinates: AP -6.9 , L 4.1 , 2.2 – 2.5 ventral from dura), and in pharmacologically treated rats additionally a cannula (coordinates AP -0.8 , L 1.6 from bregma) into the lateral ventricle of the right hemisphere. During preparation the population-spike amplitude (PSA) was optimized by delivering test pulses (A-M Systems, Isolated Pulse Stimulator, Model 2100). The animals were allowed at least 1 wk to recover from surgery.

Connecting the electrodes to a swivel by a flexible cable allowed the rats to move freely in a recording box (40 cm $\times$ 40 cm $\times$ 40 cm). The responses were amplified (differential amplifier, Inh, Science Products), transformed by an analog/digital interface (CED 1401+,

Cambridge Electronic Design), and stored on a personal computer. An input/output curve was performed 16–17 h before tetanus by recording the average of three stimuli with an intensity of 0.1 – 0.8 mA in steps of 0.1 mA. Biphasic constant current pulses (0.1 msec per half-wave) were applied to the perforant path in order to evoke DG field potentials of $\sim 40\%$ of the maximum PSA. After recording a stable baseline for 1 h (every 15 min), early LTP was induced by weak tetanic bursts (three bursts of 15 pulses of 200 Hz with 0.1 -msec duration of each stimulus and 10-sec interburst interval) at the same stimulus intensity as used for the test stimuli (0.2 – 0.4 mA). Initially after 2 min and then every 15 min after tetanization, five test stimuli (10-sec interpulse interval) were applied, and the mean values of field potentials were stored for 8 h. For analysis and presentation, 1-h values were averaged over every four 15-min values. The next day four 15-min values were averaged for a 24-h value. The 2-min value controlled for the achievement of a sufficient initial potentiation.

Holeboard apparatus and procedure

The test apparatus consisted of a black board (1 m $\times$ 1 m) with 36 regularly arranged holes (6 cm in diameter and 8 cm deep) and transparent Plexiglas walls of 27-cm height around it (COGITAT by Cognitron GmbH). Technical equipment and furniture served as distal visual cues; additional cues were fixed on the outside of the Plexiglas walls. Photobeams were mounted at the surface, at the middle, and on the ground of each hole. The holes were baited with standard food pellets (dustless precision pellets, 45 mg, BioServ). Signals of the photobeams were registered, counted, and stored on a personal computer by RatMemory V2.4 software (Heim et al. 2002).

During experiments animals were transferred to the holeboard room into a start box. The box was opened, and the animals entered the test arena. Inspections were indicated by breakings of the surface beams; visits were counted if by breaking of the beams in the middle of the holes. Finding and removal of the pellets were indicated by breaks of the ground beam. A trial was automatically stopped after 2 min or when the animal had found all pellets. The time to find all pellets (latencies), the working memory errors (inspecting or visiting a hole that has been baited but that was already inspected or visited and the pellet picked up during a specific trial), and the reference memory errors (inspecting or visiting a hole that was unbaited) were counted. After each trial, the animals were transferred back into the recording chambers. The board was cleaned with water if an animal urinated or defecated. Beneath the holeboard, there was a second board on which food pellets were scattered randomly to avoid odor information from baited holes.

All experimental and control animals received a spatial training on a fixed pattern of baited holes (cf. Fig. 1) over 10 trials (five trials on day 1, four trials on day 2, and the last trial on day 3, cf. Fig. 5), with a 15-min intertrial interval (cf. Uzakov et al. 2005).

Fifteen minutes before the last trial (between 8:00 am and 9:30 am), animals received a weak tetanus, and immediately after tetanization antagonists or vehicle solution were injected. During training and testing, animals were provided with two food pellets/day at random time points to avoid anticipation; access to water was ad libitum.

Pharmacology

SCH23390 (Sigma), a dopamine D1/D5-receptor antagonist (1 μ g, dissolved in saline); propranolol (Sigma), a β -adrenergic receptor antagonist (2 μ g, dissolved in saline); mifepristone

Figure 5. Experimental design. I/O indicates input/output-curve; weak tet, weak tetanus.

(Sigma), an antagonist of GR (150 ng, dissolved in saline with 2% ethanol); and spironolactone (Sigma) an MR-antagonist (150 ng, dissolved in saline with 2% ethanol), were applied immediately after tetanus via Hamilton syringes (5 μ L volume over 5 min in the case of SCH23390 and propranolol, and 3 μ L over 3 min in the case of mifepristone and spironolactone). The substances in these concentrations have been shown not to affect PSA baseline levels (Seidenbecher et al. 1997; Frey et al. 2001; Korz and Frey 2003). For all groups, a time-matched group (for MR and GR blockers partly overlapping) that received the same volume of vehicle served as controls.

Statistics

The general linear model for repeated measures was used for group comparisons in LTP (P -values for pairwise comparisons were Bonferroni-corrected) and one-way ANOVA for comparisons in behavior (Dunnett's-T tests as post hoc tests for pairwise comparisons). All tests were two-tailed, and the level of significance was set at $P \leq 0.05$. In all figures the means and SEM are given.

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