

# Microtubule Dynamicity Is More Important than Stability in Memory Formation: an In Vivo Study

Deyhim Atarod · Ghazaleh Eskandari-Sedighi ·  
Farid Pazhoohi · Seyyed Morteza Karimian ·  
Mojtaba Khajeloo · Gholam Hossein Riazi

Received: 13 January 2015 / Accepted: 23 February 2015 / Published online: 5 March 2015  
© Springer Science+Business Media New York 2015

**Abstract** It has been shown that microtubule (MT) activity and dynamics can have huge impacts on synaptic plasticity and memory formation. This is mainly due to various functions of MTs in neurons; MTs are involved in dendritic spine formation, axonal transportation, neuronal polarity, and receptor trafficking. Recent studies from our group and other labs have suggested the possible role of brain MT dynamicity and activity in memory; however, there is a need for more detailed studies regarding this aspect. In this study, we have tried to evaluate the importance of microtubule dynamicity rather than stability in memory formation in vivo. In order to investigate the role of MT stability in memory formation, we treated mice with paclitaxel—a classic microtubule-stabilizing agent. We then studied the behavior of treated animals using Morris water maze (MWM) test. To measure the effect of injected paclitaxel on MT polymerization kinetics, we conducted polymerization assays on brain extracts of the same paclitaxel-treated animals. Our results show that paclitaxel treatment affects animals' memory in a negative way and treated animals behave poorly in MWM compared to control group. In addition, our kinetics studies show that MT stability is significantly increased in brain extracts from paclitaxel-treated

mice, but MT dynamics is reduced. Thus, we suggest that dynamicity is a very important feature of MT protein structures, and regarding memory formation, dynamicity is more important than stability and high activity.

**Keywords** Microtubule · Microtubule dynamicity · Paclitaxel · Taxol · Memory · Synaptic plasticity

## Introduction

Learning is defined as the acquisition of information and skills, whereby subsequent retention of this information is called memory. Neuroplasticity, which is defined as the capacity of neural cells in forming new connections or modifying the ones they have, plays a crucial role in memory formation (Milner et al. 1998). Numerous studies have shown that microtubules (MTs) are essential for many of the neural cells' main functions, such as axonal transportations and receptor trafficking (Paulson and McClure 1974; Kim and Lisman 2001; Malinow and Malenka 2002; Lau and Zukin 2007). MTs are also important for neural cell polarity and dendritic spine development (Arimura and Kaibuchi 2007; Gu et al. 2008). Instability of MT structure and decrease in their total mass are observed in various neurodegenerative diseases mainly referred to as tauopathies. MT instability is strongly related to the pathological features observed in molecular level in these neurodegenerative disorders (Hasegawa et al. 1998; Falnikar and Baas 2009). Moreover, It has been described that nonfatal doses of colchicine, as a microtubule depolymerizing agent, can cause amnesia in rats, and such animals can be used as a potential animal model for studying the early stages of Alzheimer's disease (AD) (Nakayama and Sawada 2002).

---

D. Atarod · G. Eskandari-Sedighi · M. Khajeloo · G. H. Riazi (✉)  
Department of Biochemistry, Institute of Biochemistry and  
Biophysics (IBB), University of Tehran, Qods Street,  
Tehran 1417614411, Iran  
e-mail: ghriazi@ibb.ut.ac.ir

F. Pazhoohi  
Department of Animal Sciences, Shiraz University, Shiraz, Iran

S. M. Karimian  
Department of Physiology, Tehran University of Medical Sciences,  
Tehran, Iran

Microtubule is a polymer of alpha and beta tubulin. The assembly of tubulin protein resulting in microtubule formation is a dynamic process in which heterodimers of tubulin go through continuous assembly and disassembly. This dynamicity is an important characteristic of microtubules and is critical for their proper function (Desai and Mitchison 1997). Although, in neurons, MTs seemed to be less dynamic than other cells—mainly due to the impact of microtubule-associated proteins (MAPs) such as Tau protein (Brandt et al. 2005; Fanara et al. 2007)—there is growing evidence suggesting the importance of MT dynamicity in memory formation and learning. Dynamic MTs are shown to be involved in both dendritic spine changes and synaptic plasticity (Jaworski et al. 2009) as well as dendritic spine morphology and function (Hu et al. 2008). It has also been reported that changes in turnover of neuronal MTs, which demonstrate the instability of MTs, are necessary for synaptic plasticity and memory formation (Fanara et al. 2010). Moreover, a growing body of evidence suggests that the distribution of MTs in neurons is altered during long-term potentiation (LTP), which is the most well-accepted model of memory formation (Mitsuyama et al. 2007).

Paclitaxel (PT), also known as taxol, is a well-known chemotropic drug that mainly targets MT proteins and thus is used as an anticancer drug in a wide range of cancers (Rowinsky 1997; Blagosklonny and Fojo 1999). PT inhibits mitosis in proliferating cells by stabilizing microtubules (Long and Fairchild 1994), and it binds to polymerized tubules, rather than free tubulin dimers. This interaction will result in suppression of MT depolymerization and increase of MT stability, but as a consequence, it also negatively affects MT dynamics (Arnal and Wade 1995; Yvon et al. 1999). PT also stabilizes microtubule filaments against *in vitro* depolymerizing factors such as temperature drop and high concentrations of  $\text{Ca}^{2+}$  (Collins and Vallee 1987; Xiao et al. 2006).

Since PT stabilizes MT structures, some believe that it could be a good candidate to substitute Tau protein and recover MT stability that is lost upon hyperphosphorylation and aggregation of tau in tauopathies. However, the main effects of this drug in normal neurons as well as its impact on memory formation are not well studied yet (Zhang et al. 2005).

Considering previous reports and studies on the direct role of MT dynamicity in synaptic plasticity and memory formation, we decided to further investigate this matter. Our goal in this study was to examine the role of MT stability and dynamics in memory formation in mice. To reach this goal, we treated mice with PT (microtubule stabilizing agent) and then studied these animals' behavior using Morris water maze spatial memory test (MWM). Afterwards, we did some molecular studies on the brain extracts of the same animals, measuring MT polymerization kinetics, activity, and dynamicity.

## Materials and Methods

### Chemicals

Chemicals and buffers were obtained from Merck Chemical Co. GTP and ATP were supplied from Sigma-Aldrich Chemical Co. PT was provided from Stragen.

### Animals

Male BALB/C mice were obtained from the Animal Center of Institute of Biochemistry and Biophysics (IBB), University of Tehran. Animals were housed in standard cages (seven in each cage) with free access to food (standard laboratory rodent's chow) and water *ad libitum*. The animal house temperature was maintained at  $23 \pm 3$  °C with a relative humidity and 12-h light/dark cycle (light on from 06:00 to 18:00). The procedures were performed in accordance with international guidelines for animal care and use (NIH publication #85-23, revised in 1985). The ethical guidelines for the investigation of experimental animals were followed in all tests. All efforts were made to minimize animal suffering and to reduce the number of animals. Animals were transferred to the laboratory at least 1 h before the start of the experiment, and all experiments were carried out from 08:00 am to 11:00 am.

### PT Treatments

Twenty-eight male mice (weighting between 28 and 32 g) were divided into four testing groups: one control group and three drug-treated groups ( $n=7$ ). Paclitaxel dilutions (6 mg/ml) were prepared using double-distilled water. Drug-treated mice received 1, 3, and 6 mg/kg PT. The control group was only treated with the solvent (99 % DDW and 1 % ethanol). Animals were introduced to the environment 7 days before the beginning of the tests. All injections were done intraperitoneally (IP) and repetitively 90 min before the beginning of each trial test.

### Morris Water Maze

The Morris water maze (MWM) was conducted as it is described previously with a minor modification (Nakayama and Sawada 2002). The apparatus used was a circular black pool (130 cm in diameter and 30 cm in height) positioned at the middle of a large isolated room with several three-dimensional cues (e.g. shelf, desk, closet, tree) in appropriate positions that were easily visible from inside the pool. These cues and their positions were unchanged during the experiments. The transparent platform (10 cm in diameter and 15 cm in height) was located at the middle of a quadrant with equal distance from the middle and edge of the pool. It was hidden 1.5 cm beneath

the water surface (water temperature 21 °C) so that mice could easily get and stay on it.

The experiments were performed in six continuous days; 4 days of training trials, 1 day for additive trial test, and 1 day for probe test. Throughout the training trials, mice were introduced into the pool from the same point—the quadrant in the opposite side of the platform quadrant. Each mouse commenced trial at the edge of the pool, facing the wall. This starting point remained unchanged during the trial tests. For each animal, three factors were recorded: the amount of time spent to find the platform (latency), the distance animal swam before finding it (distance), and the swimming speed (velocity). Each mouse was given at most 180 s to find the platform. Once the animal found the platform, it was allowed to stay on it for 30 s before being returned to its cage. If the animal was incapable of finding the platform in 180 s, it was taken and placed on the platform and allowed to remain there for the same time (30 s).

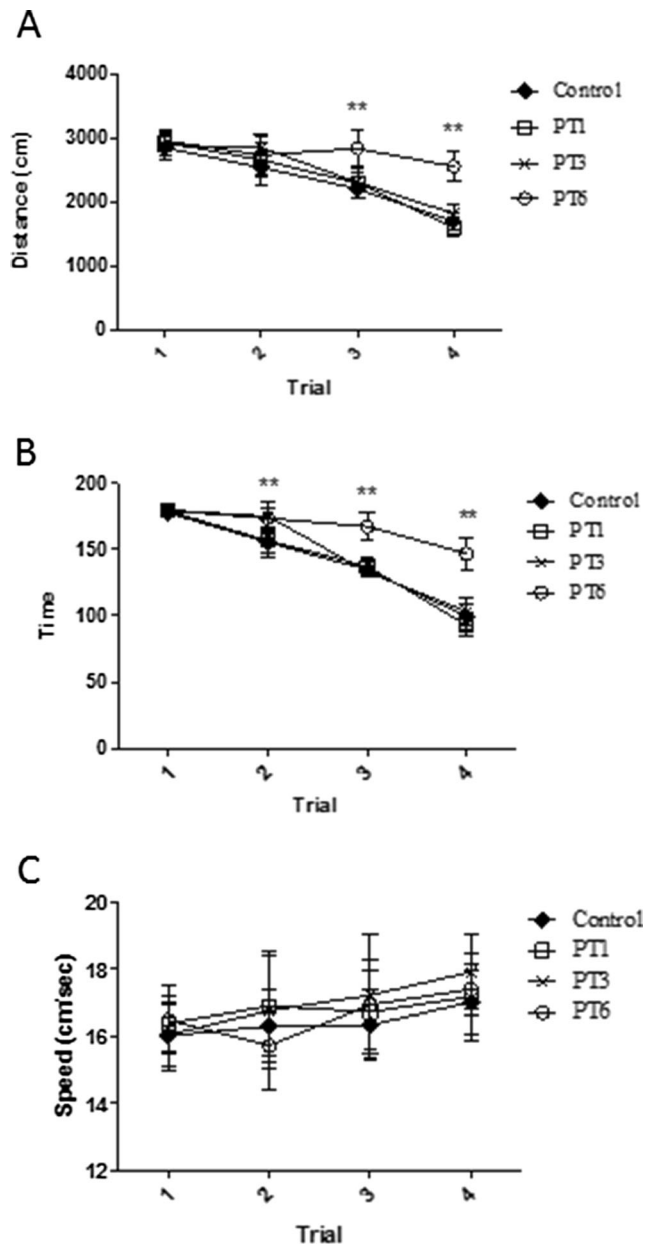
On the fifth day of the experiment, additive training trial was performed. In this additional training test, the same parameters (latency, distance, and velocity) were recorded. However, the starting point was changed to the adjacent left quadrant of the platform quadrant.

On the following day, the spatial probe test was conducted and the starting point was returned to the same position as the four training trial days. For spatial probe test, the platform was removed and the mice were let to swim for 60 s. The time each animal spent in each quadrant of the pool was recorded and reported as a percentage over 60 s.

Microtubule Polymerization Assay in Semi-purified Extract

Microtubule polymerization assay in semi-purified brain extract was done as previously described (Qian et al. 1993). Briefly, right after completion of the probe test, mice were anesthetized with chloroform and their brains were quickly removed. Medulla and cerebellum were discarded, and the remaining parts of the brains were then homogenized in cold PEM buffer (containing 0.1 M Pipes, 1 mM EGTA and 1 mM MgSO<sub>4</sub>, 0.1 M MgATP) pH 6.90, 4 °C. After homogenizing the brains on ice for 30 min, the samples were centrifuged at 100,000×g for 30 min at 4 °C. The supernatant which contained tubulin protein, GTP, MAPs, as well as several other small molecules was then taken (this will be referred to as brain extract containing tubulin (BET)). To analyze the assembly of microtubules, the increase in turbidity of BETs was measured at 350 nm at 37 °C using a carry 100 spectrophotometer. The slope of the logarithmic phase of each recorded graph—which is an indicator of how fast the MT assembly occurs—was calculated and defined as the rate of polymerization (minimum accepted *R* square was 0.94). The maximum absorbance in 350 nm was recorded as an indicator of the final total mass of microtubules. In order to investigate the

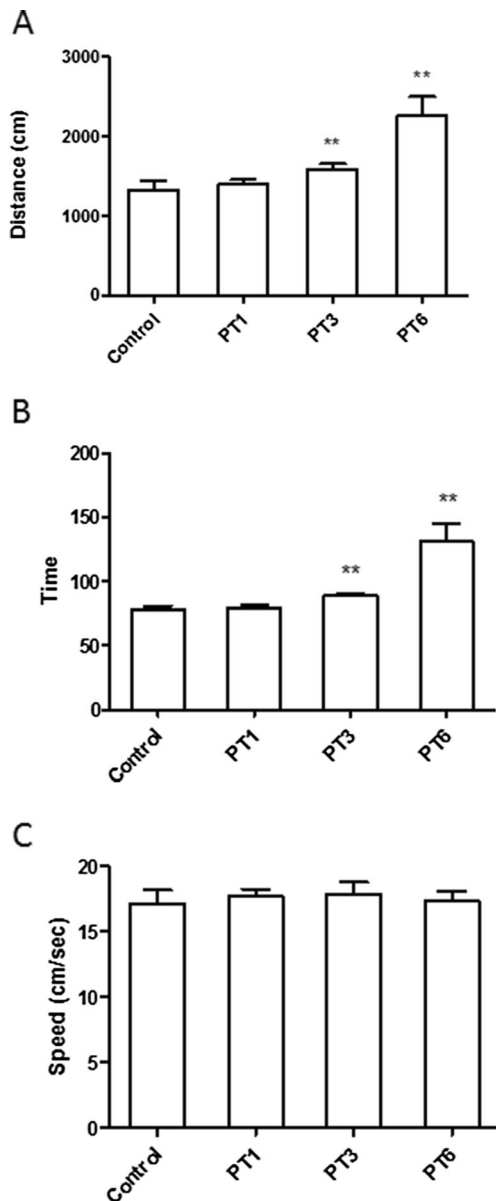
microtubule stability and dynamicity, 20 min after first polymerization, the temperature was reduced to 4 °C and MT depolymerization was recorded. The temperature-dependent microtubule disassembly went on for at least 15 min. In order to obtain numerical parameters for resistance of microtubules to temperature reduction, the minimum 350-nm absorbance was recorded and the slope of graphs was then calculated.



**Fig. 1** Trials performed in four continuous days. **a** The mean value of the swimming distance (distance), **b** the mean value of escape latency (time), and **c** the mean value of swimming velocity (speed) in control and paclitaxel-treated animals: paclitaxel 1 mg/kg (PT1), paclitaxel 3 mg/kg (PT3), and paclitaxel 6 mg/kg (PT6). Asterisks indicate significant differences (\**P*<0.05, \*\**P*<0.01 compared with the control; Dunnett’s test using ranked data or Dunnett’s test following two-way ANOVA) (*n*=7 in each group)

## Statistical Analysis

For MWM, three effects (dose, trial, and dose  $\times$  trial) were examined by two-way ANOVA, and interactions between experimental groups were considered as significant only when either the dose or dose  $\times$  trial effect demonstrated statistically significant differences. In case of significant difference between groups, Dunnett's test or Dunnett's test using ranked data at each trial day was carried out. In this case, following



**Fig. 2** Additive trial day. **a** The mean value of the swimming distance (distance), **b** the mean value of escape latency (time), **c** and the mean value of swimming velocity (speed) in control and paclitaxel-treated animals: paclitaxel 1 mg/kg (PT1), paclitaxel 3 mg/kg (PT3), and paclitaxel 6 mg/kg (PT6). Asterisks indicate significant differences (\* $P$ <0.05, \*\* $P$ <0.01; Dunnett's test using ranked data or Dunnett's test following ANOVA) ( $n$ =7 in each group)

two-way ANOVA, we used Dunnett's test to analyze the three recorded factors (swimming velocity, escape latency, and swimming distance) obtained from 4 days of training and 1 day of additive training trials in control and paclitaxel-treated groups. For probe test data, Dunnett's test was applied to compare each animal's presence percentage in each of the four quadrants. The significance level for statistical comparisons was set to  $P$  value <0.05.

## Results

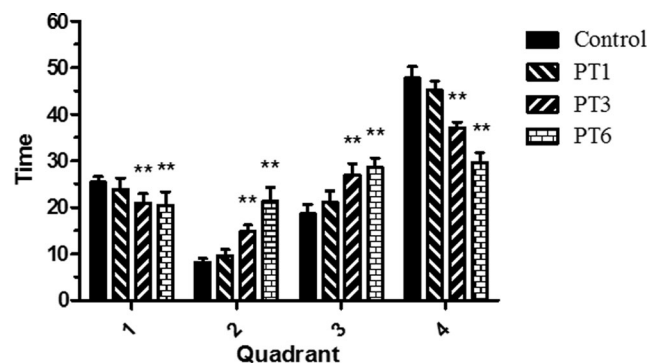
### MWM Spatial Memory Test

#### Results for Trial Test

During the trial tests, we observed significant differences in dose  $\times$  trial effects on escape latencies ( $F(9, 96)=13.76$ ,  $P$ <0.01) and swimming distance ( $F(9, 96)=6.96$ ,  $P$ <0.01) but not on swimming velocity ( $F(9, 96)=.621$ ,  $P=0.776$ ). PT treatment significantly affected escape latencies ( $F(3, 96)=61.66$ ,  $P$ <0.01) and swimming distance ( $F(3, 96)=26.30$ ,  $P$ <0.01), but had no significant effect on swimming velocity ( $F(3, 96)=1.09$ ,  $P=0.355$ ).

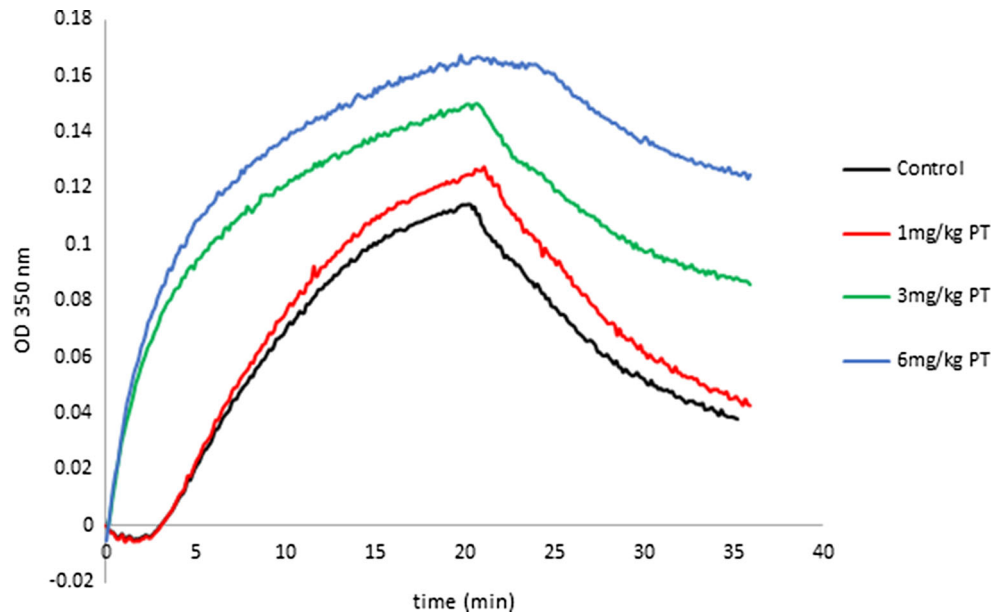
On second trial day, 3 and 6 mg/kg PT-treated animals showed a significant difference in escape latency compared to the control group ( $P$ <0.05 and  $P$ <0.01, respectively, Fig. 1b).

On trial test days 3 and 4, a significant difference was observed in the swimming distance as well as escape latency between 6 mg/kg PT-treated animals and control ( $P$ <0.01, Fig. 1a, b). No significant difference was observed for swimming velocity (Fig. 1c).



**Fig. 3** The mean value of total time spent in each quadrant by mice (percentage) in control and paclitaxel-treated animals: 1 mg/kg (PT1), 3 mg/kg (PT3), and 6 mg/kg (PT6). Quadrant 1 is the starting point; quadrants 2 and 3 are, respectively, right and left of the quadrant platform; and quadrant 4 is where platform was formerly situated. Asterisks indicate significant differences (\* $P$ <0.05, \*\* $P$ <0.01; Dunnett's test) ( $n$ =7 in each group)

**Fig. 4** MT polymerization and depolymerization kinetics in BET in control and PT-treated animals. The polymerization was performed for 20 min at 37 °C. Afterwards, temperature was dropped to 4 °C for at least 15 min to induce depolymerization. For all samples, total protein concentration was adjusted to 8 mg/ml



*Results for Additive Test*

Regarding additive trial day, escape latencies ( $F(3, 24) = 78.16, P < 0.01$ ) and swimming distance ( $F(3, 24) = 70.04, P < 0.01$ ) were significantly different in PT-treated groups compared to control group. The swimming velocity did not show any significant difference ( $F(3, 24) = 1.18, P = 0.337$ , Fig. 2c).

*Results for Probe Test*

Our results on probe day test showed that PT-treated mice (3 and 6 mg/kg) spent significantly less time in quadrants 1 and 4 ( $P < 0.01$ ), and they also spent significantly more time in quadrants 2 and 3 ( $P < 0.01$ ) compared to the control groups (Fig. 3). No significant difference was observed between the control and 1 mg/kg PT-treated animals.

**BET Microtubule Assembly Kinetics**

In order to examine the effect of injected PT on microtubule activity, we analyzed the BET prepared from the brains of the same animals used for behavioral studies. MT polymerization and depolymerization kinetics was investigated at 37 °C and

4 °C, respectively (Fig. 4). Our results showed a significant change in the kinetics of MT assembly for 3 and 6 mg/kg PT-treated mice. First of all, the nucleation phase became very short (almost undetectable) in 3 and 6 mg/kg treated mice compared to the control group. Also, the polymerization rate and maximum absorbance were significantly altered in these animals ( $P < 0.01$ ). However, not much difference was observed in 1 mg/kg PT-treated mice; the nucleation phase did not differ much with control group, and there was no major difference in polymerization rate and maximum absorbance between 1 mg/kg PT-treated animals and the control group ( $P > 0.05$ , Table. 1).

The rate of depolymerization and minimum absorbance were also significantly different in 3 and 6 mg/kg PT-treated groups in comparison to control ( $P < 0.01$ ). However, these two parameters were quite the same as control for 1 mg/kg PT-treated groups ( $P > 0.05$ , Table. 2).

**Discussion**

It is quite well accepted that synaptic plasticity has a decisive role in cognitive functions such as memory formation and learning (Martin et al. 2000). Long-term potentiation (LTP),

**Table 1** The rate of polymerization and maximum absorbance (mean values ± SDs) of MTs derived from polymerization assay kinetics at 37 °C

	Control	1 mg/kg PT	3 mg/kg PT	6 mg/kg PT
Rate of polymerization	0.0085±0.0002	0.0089±0.0003	0.0178±0.0002**	0.0209±0.0006**
Maximum absorbance	0.1158±0.0026	0.1210±0.0043	0.1516±0.0015**	0.1672±0.001**

The total protein concentration was adjusted to 8 mg/ml in all experiments. Data were obtained from three repeats. Asterisks indicate significant differences (\* $P < 0.05$ , \*\* $P < 0.01$  compared with control; Student’s *T* test)



**Table 2** The rate of depolymerization and minimum absorbance (mean values  $\pm$  SDs) of MTs derived from depolymerization kinetics assay at 4 °C

	Control	1 mg/kg PT	3 mg/kg PT	6 mg/kg PT
Rate of depolymerization	0.0052 $\pm$ 0.0002	0.0056 $\pm$ 0.0002	0.0043 $\pm$ 0.0003**	0.0030 $\pm$ 0.0001**
Minimum absorbance	0.0386 $\pm$ 0.0008	0.0403 $\pm$ 0.0012	0.0853 $\pm$ 0.0009**	0.1223 $\pm$ 0.0026**

The total protein concentration was adjusted to 8 mg/ml in all experiments. Data were obtained from three repeats. Asterisks indicate significant differences (\* $P$ <0.05, \*\* $P$ <0.01 compared with control; Student's  $T$  test)

which is a well-characterized form of synaptic plasticity, is mainly influenced by two cellular events: up-regulation of AMPA and NMDA receptors in the synaptic membrane of post-synaptic neurons and formation of new synapses between neurons (Lynch 2004; Cooke and Bliss 2006). MT activity and dynamics is directly involved in both of these cellular events (Collingridge et al. 2004; Jaworski et al. 2009). Previously, it has been suggested that MT-stabilizing agents such as PT could improve the function of neurons under specific circumstances where MT network is disturbed (for example in tauopathies such as AD) (Michaelis et al. 1998; Zhang et al. 2005). Under these conditions, MTs are pretty unstable mainly due to hyperphosphorylation and aggregation of tau protein, which is a natural MAP responsible for stabilizing MT network (Nakayama and Sawada 2002; Ballatore et al. 2007). As a result, it has been suggested that MT-stabilizing agents could be good substitutions for malfunctioning Tau protein, to prevent MT instability and disassembly (Matsuoka et al. 2008).

On the other hand, MTs are dynamic structures, and various reports suggest that this dynamicity is a critical characteristic for their proper function (Desai and Mitchison 1997). A previous study in our lab has also shown that chronic social stress conditions, that can significantly suppress learning and memory, has had a huge negative effect on MT's dynamicity in the brain cortex of rats (Eskandari-Sedighi et al. 2014). Accordingly, we presumed that the dynamicity of MT network is a more critical feature than its stability, especially regarding memory formation.

Our behavioral study results demonstrate that 1 mg/kg of PT does not seem to have any special effect on memory. MT polymerization kinetics and calculated parameters of MT polymerization and depolymerization have remained unchanged in 1 mg/kg PT-treated mice compared to control groups. This could be due to the low ability of PT to cross the blood–brain barrier (Fellner et al. 2002). However, higher doses of PT (3–6 mg/kg) have had significant negative effects on animals' behavior in MWM experiment in comparison to the control group. Our MT polymerization kinetics studies also showed that the rate of MT polymerization, as well as the total mass of MTs in BET, has remarkably increased in 3 and 6 mg/kg PT-treated mice. MTs were firmly stable, and they were resistant to *in vitro* depolymerizing conditions (temperature dropping from 37 to 4 °C). The activity of MTs was also noticeably

similar to previous *in vitro* studies (Schiff et al. 1979; Collins and Vallee 1987). All these results strongly suggest that PT treatment can result in an increase in stability of MTs and their total mass, but MT dynamics will be considerably reduced.

Our studies also revealed that PT-treated mice behaved poorly in MWM compared to the control groups, suggesting that despite an increase in stability of MTs and total mass, animal's memory was not enhanced. This observation strongly supports the idea that MT dynamicity is a more critical characteristic than its stability regarding memory formation. MTs are directly involved in receptor trafficking and dendritic spine formation in neurons (Collingridge et al. 2004; Jaworski et al. 2009), and this needs new, continuous arrangement of MT network within neurons. A decrease in dynamicity brings more rigidity to MTs, and extreme rigidity can then have a negative effect on the whole system.

Our results also revealed that despite the fact that the blood–brain barrier is not so permeable to PT, even low amounts of PT that can pass through it will still have a big influence on memory. This is probably because of the high affinity of PT for MT proteins.

In conclusion, our work demonstrates that systemic injection of PT can have a negative effect on mice memory formation. According to our results, MT dynamicity seems to be a more important feature than MT total mass, high activity, and stability. We, as a result, suggest that the dynamicity of MTs correlates with rearrangement of these proteins' network during LTP. MT dynamicity, therefore, can influence synaptic plasticity, and this seems to be a more critical point than the network stability regarding memory formation.

## References

- Arimura N, Kaibuchi K (2007) Neuronal polarity: from extracellular signals to intracellular mechanisms. *Nat Rev Neurosci* 8(3):194–205
- Arnal I, Wade RH (1995) How does taxol stabilize microtubules? *Curr Biol* 5(8):900–908
- Ballatore C, Lee VM-Y, Trojanowski JQ (2007) Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci* 8(9):663–672
- Blagosklonny MV, Fojo T (1999) Molecular effects of paclitaxel: myths and reality (a critical review). *Int J Cancer* 83(2):151–156

- Brandt R, Hundelt M, Shahani N (2005) Tau alteration and neuronal degeneration in tauopathies: mechanisms and models. *Biochim Biophys Acta (BBA)-Mol Basis Dis* 1739(2):331–354
- Collingridge GL, Isaac JT, Wang YT (2004) Receptor trafficking and synaptic plasticity. *Nat Rev Neurosci* 5(12):952–962
- Collins CA, Vallee RB (1987) Temperature-dependent reversible assembly of taxol-treated microtubules. *J Cell Biol* 105(6):2847–2854
- Cooke S, Bliss T (2006) Plasticity in the human central nervous system. *Brain* 129(7):1659–1673
- Desai A, Mitchison TJ (1997) Microtubule polymerization dynamics. *Annu Rev Cell Dev Biol* 13(1):83–117
- Eskandari-Sedighi G, Hossein Riazi G, Reza Vaez Mahdavi M, Cheraghi T, Atarod D, Rafiei S (2014) Chronic, long-term social stress can cause decreased microtubule protein network activity and dynamics in cerebral cortex of male Wistar rats. *J Mole Neurosci* 55(3):579–586
- Falnikar A, Baas PW (2009) Critical roles for microtubules in axonal development and disease. Springer, *Cell Biology of the Axon*, pp 47–64
- Fanara P, Banerjee J, Hueck RV, Harper MR, Awada M, Turner H, Husted KH, Brandt R, Hellerstein MK (2007) Stabilization of hyperdynamic microtubules is neuroprotective in amyotrophic lateral sclerosis. *J Biol Chem* 282(32):23465–23472
- Fanara P, Husted K, Selle K, Wong P-Y, Banerjee J, Brandt R, Hellerstein M (2010) Changes in microtubule turnover accompany synaptic plasticity and memory formation in response to contextual fear conditioning in mice. *Neuroscience* 168(1):167–178
- Fellner S, Bauer B, Miller DS, Schaffrik M, Fankhänel M, Spruß T, Bernhardt G, Graeff C, Färber L, Gschaidmeier H (2002) Transport of paclitaxel (Taxol) across the blood–brain barrier in vitro and in vivo. *J Clin Invest* 110(9):1309–1318
- Gu J, Firestein BL, Zheng JQ (2008) Microtubules in dendritic spine development. *J Neurosci* 28(46):12120–12124
- Hasegawa M, Smith MJ, Goedert M (1998) Tau proteins with FTDP-17 mutations have a reduced ability to promote microtubule assembly. *FEBS Lett* 437(3):207–210
- Hu X, Viesselmann C, Nam S, Merriam E, Dent EW (2008) Activity-dependent dynamic microtubule invasion of dendritic spines. *J Neurosci* 28(49):13094–13105
- Jaworski J, Kapitein LC, Gouveia SM, Dortland BR, Wulf PS, Grigoriev I, Camera P, Spangler SA, Di Stefano P, Demmers J (2009) Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. *Neuron* 61(1):85–100
- Kim C-H, Lisman JE (2001) A labile component of AMPA receptor-mediated synaptic transmission is dependent on microtubule motors, actin, and N-ethylmaleimide-sensitive factor. *J Neurosci* 21(12):4188–4194
- Lau CG, Zukin RS (2007) NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nat Rev Neurosci* 8(6):413–426
- Long BH, Fairchild CR (1994) Paclitaxel inhibits progression of mitotic cells to G1 phase by interference with spindle formation without affecting other microtubule functions during anaphase and telophase. *Cancer Res* 54(16):4355–4361
- Lynch M (2004) Long-term potentiation and memory. *Physiol Rev* 84(1):87–136
- Malinow R, Malenka RC (2002) AMPA receptor trafficking and synaptic plasticity. *Annu Rev Neurosci* 25(1):103–126
- Martin S, Grimwood P, Morris R (2000) Synaptic plasticity and memory: an evaluation of the hypothesis. *Annu Rev Neurosci* 23(1):649–711
- Matsuoka Y, Jouroukhin Y, Gray AJ, Ma L, Hirata-Fukae C, Li H-F, Feng L, Lecanu L, Walker BR, Planel E (2008) A neuronal microtubule-interacting agent, NAPVSIPQ, reduces tau pathology and enhances cognitive function in a mouse model of Alzheimer’s disease. *J Pharmacol Exp Ther* 325(1):146–153
- Michaelis M, Ranciat N, Chen Y, Bechtel M, Ragan R, Hepperle M, Liu Y, Georg G (1998) Protection against  $\beta$ -amyloid toxicity in primary neurons by paclitaxel (Taxol). *J Neurochem* 70(4):1623–1627
- Milner B, Squire LR, Kandel ER (1998) Cognitive neuroscience and the study of memory. *Neuron* 20(3):445–468
- Mitsuyama F, Futatsugi Y, Okuya M, Karagiozov K, Kato Y, Kanno T, Sano H, Koide T (2007) Microtubules to form memory. *Italian journal of anatomy and embryology=Archivio italiano di anatomia ed embriologia* 113(4):227–235
- Nakayama T, Sawada T (2002) Involvement of microtubule integrity in memory impairment caused by colchicine. *Pharmacol Biochem Behav* 71(1):119–138
- Paulson JC, McClure WO (1974) Microtubules and axoplasmic transport. *Brain Res* 73(2):333–337
- Qian A, Burton P, Himes R (1993) A comparison of microtubule assembly in brain extracts from young and old rats. *Mol Brain Res* 18(1):100–106
- Rowinsky M, Eric K (1997) The development and clinical utility of the taxane class of antimicrotubule chemotherapy agents. *Annu Rev Med* 48(1):353–374
- Schiff PB, Fant J and Horwitz SB (1979) Promotion of microtubule assembly in vitro by taxol. *Nature* 277:665–667
- Xiao H, Verdier-Pinard P, Fernandez-Fuentes N, Burd B, Angeletti R, Fiser A, Horwitz SB, Orr GA (2006) Insights into the mechanism of microtubule stabilization by Taxol. *Proc Natl Acad Sci* 103(27):10166–10173
- Yvon A-MC, Wadsworth P, Jordan MA (1999) Taxol suppresses dynamics of individual microtubules in living human tumor cells. *Mol Biol Cell* 10(4):947–959
- Zhang B, Maiti A, Shively S, Lakhani F, McDonald-Jones G, Bruce J, Lee EB, Xie SX, Joyce S, Li C (2005) Microtubule-binding drugs offset tau sequestration by stabilizing microtubules and reversing fast axonal transport deficits in a tauopathy model. *Proc Natl Acad Sci U S A* 102(1):227–231