Supporting Information

Epinephrine destabilizes the Alzheimer's disease-related tau protofibril and fibril: A computational study

Jiaxing Tang[a], Dushuo Feng[b], Feng Wang[a], Lulu Guan[b], Zhengdong Xu[c], Yu Zou[b]*

[a] School of Physical Education, Xiangnan University, 889 Chenzhou Avenue, Chenzhou 423000, People's Republic of China
[b] Department of Sport and Exercise Science, College of Education, Zhejiang University, 866 Yuhangtang Road, Hangzhou 310058, Zhejiang, People's Republic of China
[c] Department of Physical Education, Shanghai University of Engineering Science, 333 Long Teng Road, Shanghai, 201620, People's Republic of China

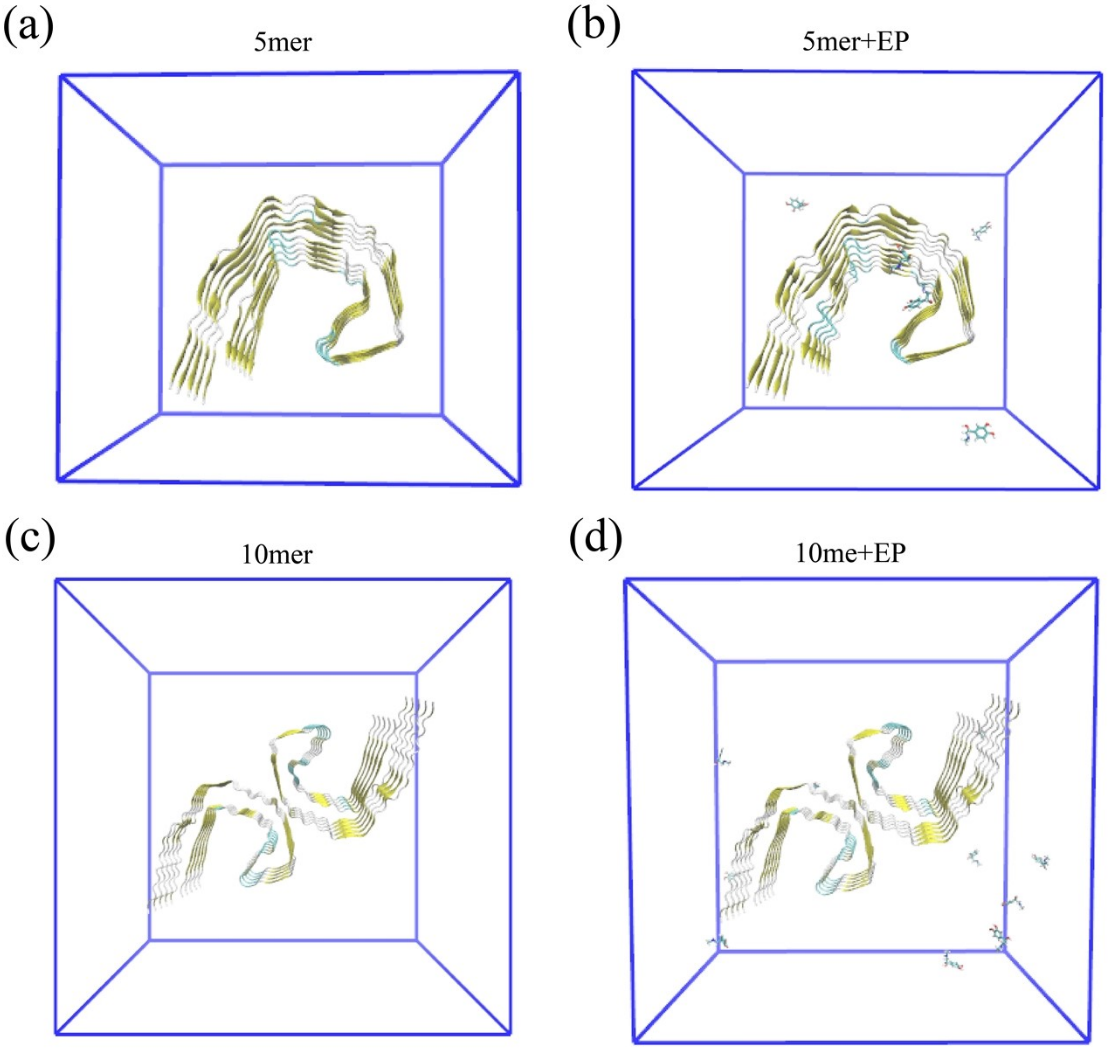

Figure S1. Initial states of the AD-related tau protofibril/fibril in the absence (a, c) and presence (b, d) of EP molecules.

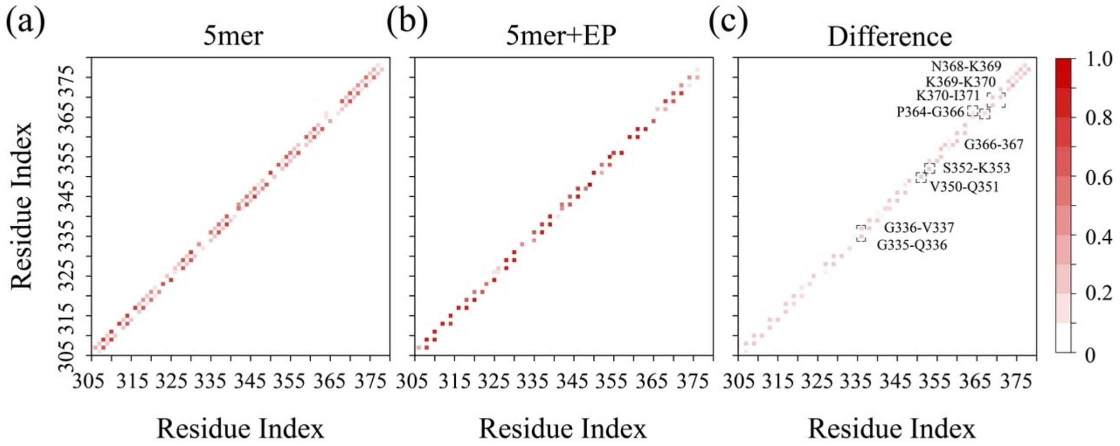

Figure S2. Interchain MC H-bond network of the AD-related tau protofibril in the 5mer (a) and 5mer+EP (b) systems. The difference (5mer minus 5mer+EP) of the interchain MC H-bond between the two systems (c).

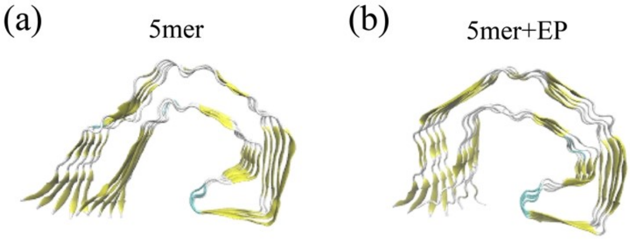

Figure S3. The representative conformations corresponding to the lowest energy basins of the protofibril in the 5mer (a) and 5mer+EP (b) systems.

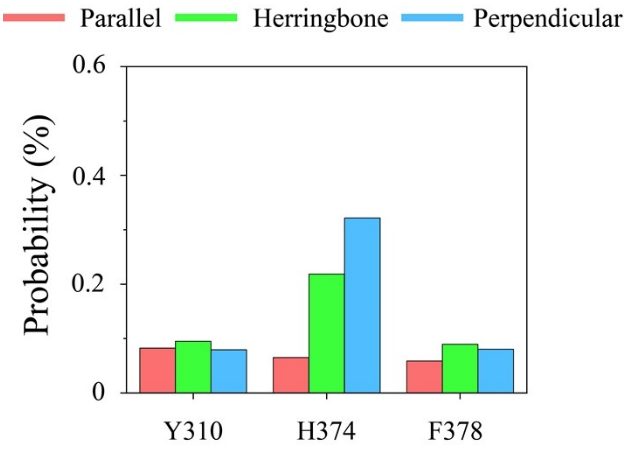

Figure S4. π-π stacking probability between EP and aromatic residues Y310/H374/F378 of the AD-related tau protofibril.

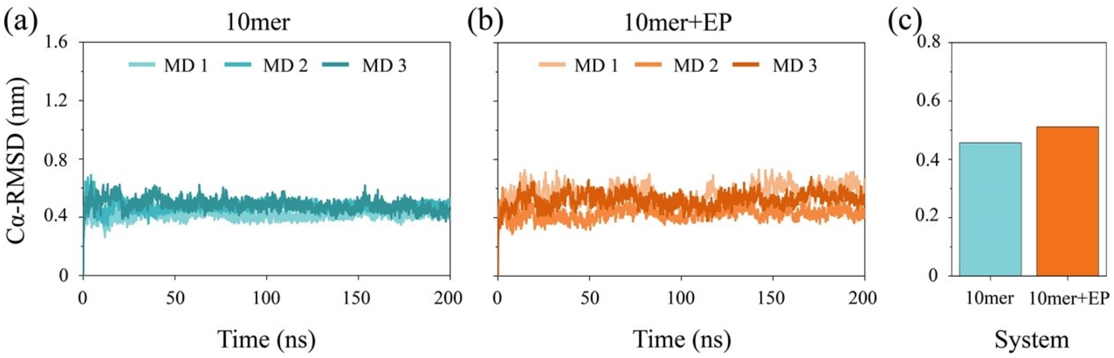

Figure S5. Time-based Cα-RMSD values for the three trajectories of the AD-related tau fibril in the 10mer (a) and 10mer+EP systems (b). Time-averaged Cα-RMSD of the fibril in the two systems (c).

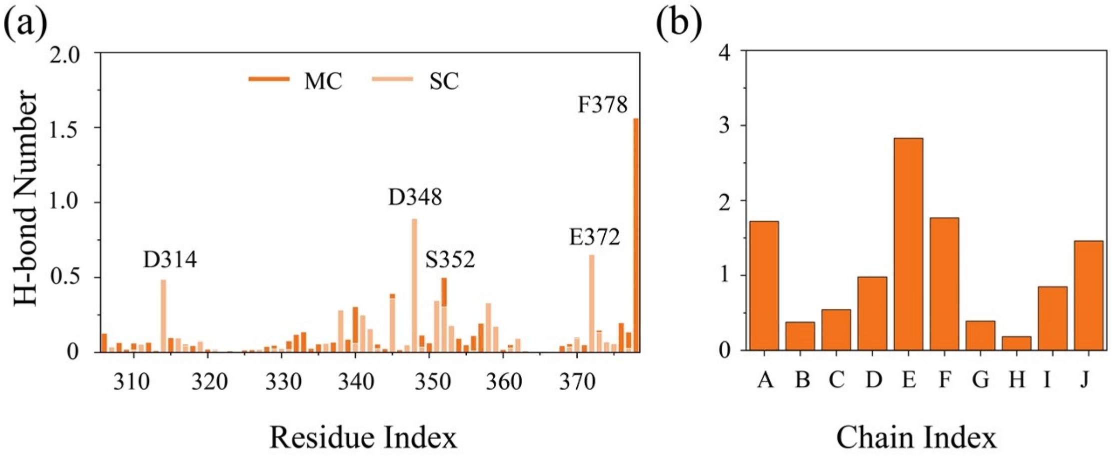

Figure S6. Residue-based MC and SC H-bond number between EP and AD-related tau fibril (a). Total H-bond number between each peptide chain of the fibril and EP (b).

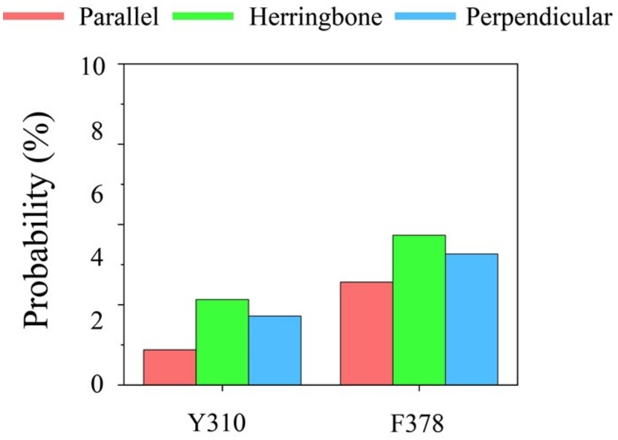

Figure S7. π-π stacking probability between EP and aromatic residues Y310/F378 of the AD-related tau fibril.

Table S1. Statistical comparison of the main parameters between 5mer and 5mer+EP systems. The data analysis was based on 400-500 ns.

	5mer (mean ± SD)	95% CI	K-S (*p*)	5mer+EP (mean ± SD)	95% CI	K-S (*p*)	MW-U (*p*)/ |*r*|
Cα-RMSD (nm)	0.34 ± 0.02	0.339-0.341	0.000	0.40 ± 0.03	0.398-0.400	0.000	0.000/0.83
Secondary structure (%)							
Coil	39.77 ± 0.88	39.73-39.81	0.000	44.07 ± 1.15	44.02-44.12	0.000	0.000/0.86
β-sheet	53.87 ± 0.99	53.82-53.91	0.000	48.68 ± 0.01	48.63-48.73	0.001	0.000/0.87
β-bridge	0.95 ± 0.26	0.94-0.96	0.000	2.04 ± 0.37	2.02-2.05	0.000	0.000/0.85
Bend	4.60 ± 0.40	4.58-4.62	0.000	4.52 ± 0.39	4.50-4.54	0.000	0.000/0.10
Turn	0.81 ± 0.31	0.80-0.82	0.000	0.69 ± 0.29	0.68-0.71	0.000	0.000/0.19
Interchain MC H-bond number	47.38 ± 0.81	47.35-47.42	0.000	44.36 ± 0.84	44.33-44.40	0.000	0.000/0.86
SASA (nm^2)	183.94 ± 1.49	183.87-184.00	0.200	188.03 ± 1.51	187.96-188.09	0.000	0.000/0.83
MC H-bond number	192.46 ± 3.32	192.31-192.60	0.001	182.05 ± 3.53	181.90-182.21	0.002	0.000/0.84

SD: standard deviation; CI: confidence interval; K-S: Kolmogorov-Smirnov test; MW-U: Mann-Whitney U Test; Pearson's *r* (*r*): effect size for MW-U.

Table S2. Statistical comparison of the main parameters between 10mer and 10mer+EP systems. The data analysis was based on 100-200 ns.

	10mer (mean ± SD)	95% CI	K-S (*p*)	10mer+EP (mean ± SD)	95% CI	K-S (*p*)	MW-U (*p*)/|*r*|
Cα-RMSD	0.46 ± 0.02	0.456-0.457	0.000	0.51 ± 0.03	0.510-0.513	0.001	0.000/0.76

(nm)							
Secondary structure (%)							
Coil	38.89 ± 0.77	38.86-38.93	0.001	40.78 ± 0.70	40.74-40.81	0.011	0.000/0.80
β-sheet	53.37 ± 0.92	53.33-53.41	0.004	50.36 ± 0.82	50.33-50.40	0.037	0.000/0.85
β-bridge	1.25 ± 0.27	1.23-1.26	0.000	1.30 ± 0.26	1.29-1.31	0.000	0.000/0.10
Bend	5.57 ± 0.31	5.55-5.58	0.000	6.81 ± 0.34	6.80-6.83	0.000	0.000/0.86
Turn	0.92 ± 0.22	0.91-0.93	0.000	0.70 ± 0.20	0.70-0.71	0.000	0.000/0.47
P-P contact number	62267.11 ± 122.28	62261.75-62272.47	0.200	62061.74 ± 129.07	62056.08-62067.40	0.200	0.000 (t)/1.63(*d*)
SASA (nm^2)	344.37 ± 1.93	344.28-344.45	0.200	349.74 ± 1.98	349.66-349.83	0.200	0.000 (t)/3.58 (*d*)
Inter-protofibril CSA (nm^2)	24.59 ± 0.47	24.57-24.61	0.133	24.77 ± 0.44	24.75-24.79	0.027	0.000/0.19

SD: standard deviation; CI: confidence interval; K-S: Kolmogorov-Smirnov test; MW-U: Mann-Whitney U Test; t: Student's t-test; Pearson's *r* (*r*): effect size for MW-U; *d*: Cohen's *d*.

Table S3. Secondary structure composition probability of the AD-related tau protofibril for the three trajectories in the 5mer and 5mer+EP systems.

	5mer			5mer + EP		
	MD1	MD2	MD3	MD1	MD2	MD3
Coil (%)	40.79	40.70	37.83	43.38	45.92	42.90
β-sheet (%)	52.21	52.65	56.74	48.99	46.54	50.51
β-bridge (%)	1.75	0.81	0.30	2.26	2.42	1.44
Bend (%)	4.53	5.15	4.12	4.80	4.31	4.45
Turn (%)	0.73	0.69	1.01	0.57	0.81	0.71

Table S4. Secondary structure composition probability of the AD-related tau fibril for the three trajectories in 10mer and 10mer+EP systems.

	10mer			10mer + EP		
	MD1	MD2	MD3	MD1	MD2	MD3
Coil (%)	39.22	38.12	39.34	41.26	39.03	42.03
β-sheet (%)	54.38	52.37	53.38	51.37	51.38	48.35
β-bridge (%)	1.14	1.20	1.40	1.23	1.55	1.13
Bend (%)	4.34	7.39	4.97	5.54	7.07	7.82
Turn (%)	0.93	0.91	0.92	0.61	0.84	0.67