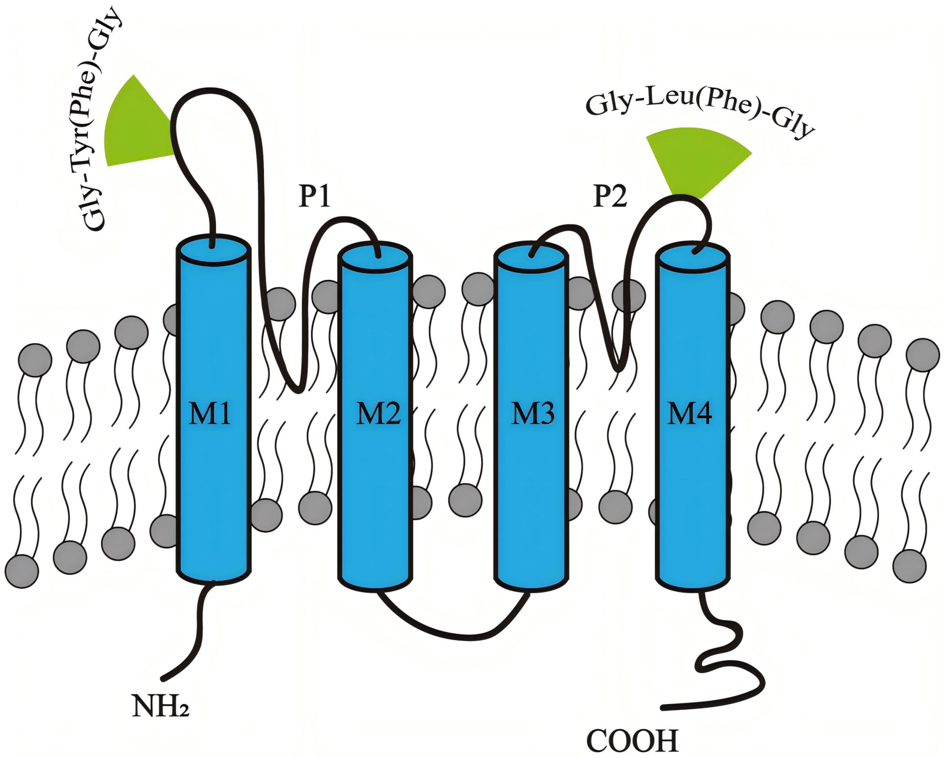
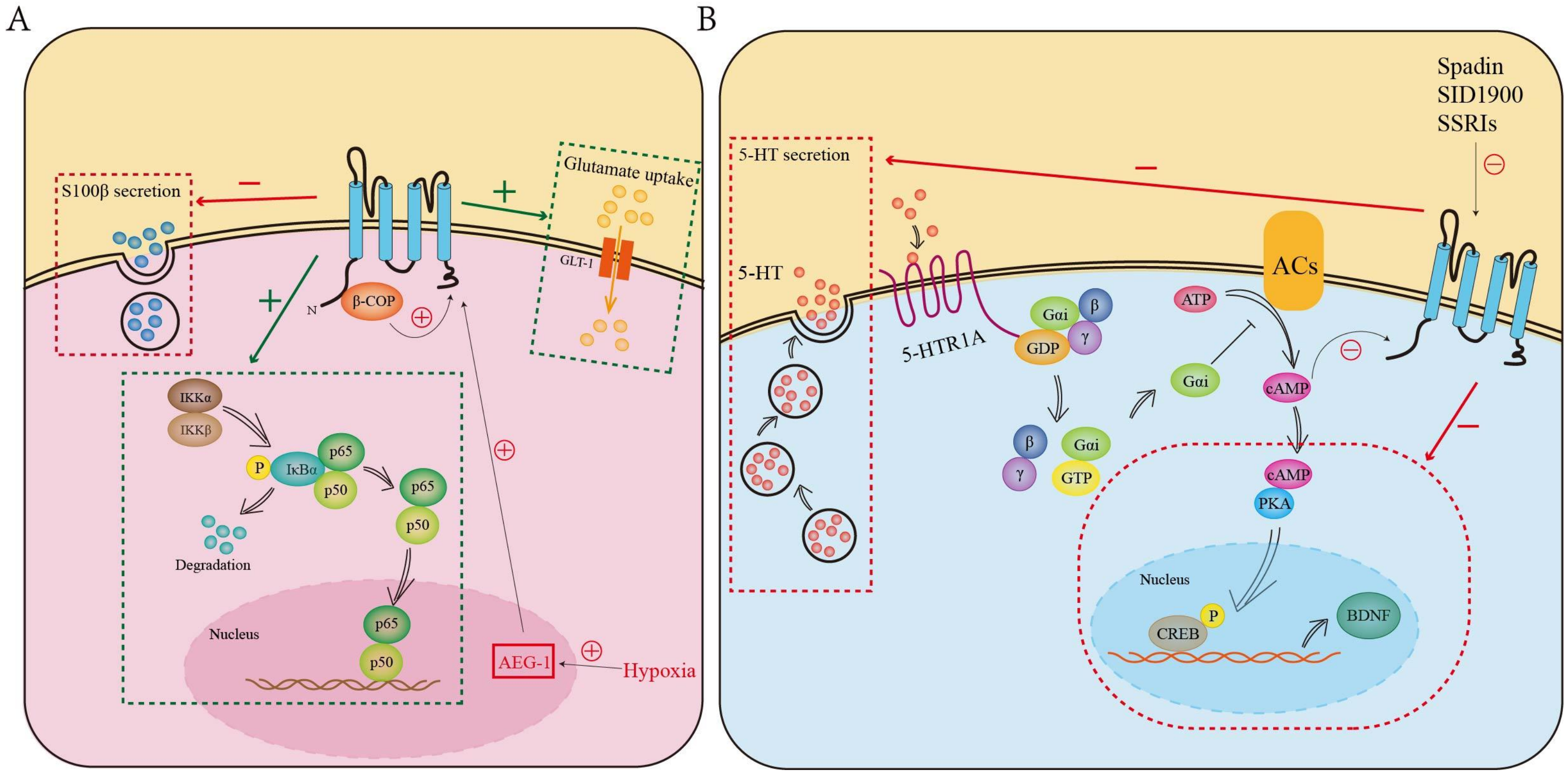


Supplementary Figure 1 | Structure of TREK-1 channel. TREK-1 channel has four transmembrane segments and two pore domains, containing an extended M1P1 extracellular loop and both amino- and carboxy-termini in the intracellular domains. What’s more, Gly-Tyr(Phe)-Gly and Gly-Leu(Phe)-Gly make up the distinctive pore signature sequence of TREK-1 channel. TREK-1: TWIK-related potassium channel.



Supplementary Figure 2 | Illustrative Mechanisms of TREK-1 Channel Function. A. Regulation of activated astrocytes by TREK-1. TREK-1 activation reduces the secretion of S100β, increases glutamate uptake, and activates the NF-κB pathway in astrocytes. B. Regulation of 5-HT Transport by TREK-1. TREK-1 activation inhibits the release of 5-HT and the production of BDNF. GLT-1: Glutamate transporter 1; AEG-1: Astrocyte elevated gene-1; β-COP: β-coat protein; 5-HT: serotonin; 5-HTR1A: 5-HT1A autoreceptors; AC: adenylate cyclase; SSRIs: Selective serotonin reuptake inhibitors; cAMP: Cyclic adenosine monophosphate; PKA: Protein kinase A; CREB: Cyclic-AMP response binding protein; BDNF: Brain-derived neurotrophic factor.

Supplementary Table 1 | TREK-1 in Cerebral ischemia

Study Type	Study subjects	Models	TREK-1 Activators	TREK-1 Inhibitors	Whether the activation of TREK-1 is beneficial ("√" means yes, "×" means no)	Reference
Animal Model Study	Rats	Forebrain ischemia	Linolenic acid	-	√	[1]
Animal Model Study	Mice	CCAs during systemic hypotension	Linolenic acid; lysophosphatidylcholine	-	√	[2]
In Vitro Study	Primary co-cultures of mixed neuron and astrocyte	Hypoxia	-	Quinine; Bupivacaine	√	[3]
In Vitro Study	SH-SY5Y human neuroblastoma cells	OGD	Sevoflurane	SiRNA to inhibit the expression of TREK-1	√	[4]
Animal Model Study	Rats	MCAO	Sevoflurane	SiRNA to inhibit the expression of TREK-1	√	[4]
Animal Model Study	Rats	MCAO	Sevoflurane	TREK-1 knockout rat	√	[5]
In Vitro Study	Primary cultures of astrocytes	OGD	Arachidonic acid	-	√	[6]
Animal Model Study	Rats	MCAO	Dexmedetomidine	SiRNA to inhibit the expression of TREK-1	√	[7]
Animal Model Study	Mice	MCAO	-	Spadin	×	[8]

In Vitro Study	Wild-type Chinese hamster ovary cells expressing rat TREK-1 channels	OGD	-	Lig4-4	×	9
Animal Model Study	Rats	MCAO	-	Lig4-4	×	9
Animal Model Study	Mice	MCAO	Mini-spadin [at low doses]	Spadin; Mini-spadin [at high doses]	-	10
In Vitro Study	PC12 cell	Ischemia	-	MTC	×	11
Animal Model Study	Rats	MCAO	-	MTC		
Animal Model Study	Mice	MCAO	-	Spadin; TREK-1 knockout mice	×	12

This table summarizes the role of TREK-1 in cerebral ischemic diseases. For the references represented by the numbers, see the references after all tables. Abbreviations: CCAs, common carotid arteries; OGD, oxygen-glucose deprivation; MCAO, middle cerebral artery occlusion; siRNA, small RNA interference.

Supplementary Table 2 | TREK-1 in Depression

Study Type	Study subjects	Models	TREK-1 Activators	TREK-1 Inhibitors	Whether the activation of TREK-1 is beneficial (“ √ ” means yes, “×” means no)	Reference
Animal Model Study	Mice	-	-	TREK-1 knockout mice	×	13
Animal Model Study	Mice	-	-	Spadin; TREK-1 knockout mice	×	14

Animal Model Study	Rats	CUMS	-	Spadin; SID1900; Citalopram	×	15
Animal Model Study	Rats	CUMS	-	Spadin; SID1900; Fluoxetine	×	16
Animal Model Study	Mice	LPS-induced depressive-like behaviors	-	Cre-dependent TREK-1 knockdown transgenic mouse	×	17
Animal Model Study	Mice	CUMS	AAV overexpressing TREK-1	Spadin; SID1900; AAV expressing a short hairpin RNA targeting the sequence of the TREK-1 gene	×	18
Animal Model Study	Rats	CUMS	-	SID1900	×	19
In Vitro Study	Rat astrocyte cell line	-	-	Spadin	×	20
Animal Model Study	Rats	CUMS	-	Spadin	×	20
Animal Model Study	Mice	-	-	NTSR3/sortilin homozygous knockout mice	×	21
Animal Model Study	Rats	PSD (MCAO+CUMS)	-	Escitalopram	×	22
Animal Model Study	Mice	SDS	Ostruthin	-	√	23
Animal Model Study	Mice	Oxaliplatin-induced	Riluzole	TREK-1 knockout mice	√	24

		depressive-like behaviors				
Animal Model Study	Mice	CUMS	Ostruthin	-	√	25

This table summarizes the role of TREK-1 in depression. For the references represented by the numbers, see the references after all tables. Abbreviations: CUMS, chronic unpredictable mild stress; LPS, lipopolysaccharide; PSD, post-stroke depression; SDS, Social defeat stress; AAV, adeno-associated virus.

Supplementary Table 3 | TREK-1 in Neuropathic Pain

Study Type	Study subjects	Models	TREK-1 Activators	TREK-1 Inhibitors	Whether the activation of TREK-1 is beneficial (“ √ ” means yes, “×” means no)	Reference
Animal Model Study	Mice	Oxaliplatin-induced neuropathy	-	TREK1-TRAAK knockout mice	√	26
Animal Model Study	Mice	Oxaliplatin-induced neuropathy	Riluzole	TREK-1 knockout mice	√	24
Animal Model Study	Mice	Oxaliplatin-induced neuropathy			√	27
Animal Model Study	Rats	Formalin-induced acute pain and long-lasting mechanical allodynia and hyperalgesia	BL-1249	Spadin	√	28
Animal Model Study	Rats	L5/L6 spinal nerve ligation-induced tactile allodynia.	BL-1249	Spadin	√	29
Animal Model Study	Rats	Prediabetic neuropathic pain	BL-1249	SiRNA to inhibit the expression of TREK-1;	√	30

Animal Model Study	Rats	Neuropathic pain-induced by chronic constriction sciatic nerve injury.	-	Spadin MiR-183-5p	×	31

This table summarizes the role of TREK-1 in neuropathic pain. For the references represented by the numbers, see the references after all tables. Abbreviations: siRNA, small RNA interference.

Supplementary Table 4 | TREK-1 in Epilepsy

Study Type	Study subjects	Models	TREK-1 Activators	TREK-1 Inhibitors	Whether the activation of TREK-1 is beneficial (" √ " means yes, " × " means no)	Reference
Animal Model Study	Mice	kainic acid-induced seizures	Linolenic acid; Lysophosphatidylcholine	-	√	2
Animal Model Study	Rats	kainic acid-induced seizures	Linolenic acid	-	√	1
In Vitro Study	CHO cells expressing human TREK-1 channels	-	-	-	√	32
Animal Model Study	Rats	Lithium-pilocarpine-induced status epilepticus	AAV overexpressing TREK-1	-	√	33
Animal Model Study	Mice	high pressure-induces recurrent epileptic seizure	-	TREK-1 knockout mice	√	34

This table summarizes the role of TREK-1 in epilepsy. For the references represented by the numbers, see the references after all tables. Abbreviations: AAV, adeno-associated virus.

Supplementary Table 5 | TREK-1 in Cognitive impairment

Study Type	Study subjects	Models	TREK-1 Activators	TREK-1 Inhibitors	Whether the activation of TREK-1 is beneficial (“ √ ” means yes, “×” means no)	Reference
Animal Model Study	Mice	Isoflurane anesthesia-induced memory impairment	AAV overexpressing TREK-1	AAV contained SiRNAs-Vector against TREK-1	×	[35]
Animal Model Study	Mice	Df(16)A$^{+/-}$ mice (Exhibits impairments in social memory)	-	Spadin; TREK-1 dominant negative virus	×	[36]
Animal Model Study	Mice	MCAO	Mini-spadin [at low doses]	Spadin; Mini-spadin [at high doses]	-	[10]
Animal Model Study	Mice	-	TREK-1 knockout mice	-	-	[37]
Animal Model Study	Mice	SAMP8 mice (Model of Alzheimer's disease)	alpha-Linolenic acid	-	√	[38]
Animal Model Study	Mice	-	-	TREK-1 knockout mice	√	[39]

This table summarizes the role of TREK-1 in cognitive impairment. For the references represented by the numbers, see the references after all tables. Abbreviations: MCAO, middle cerebral artery occlusion; AAV, adeno-associated virus; siRNA, small RNA interference.

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