TABLE 1 SUPPORTING INFORMATION

Effect of FDA-approved AD therapeutics on astrocyte function. *For mild-to-moderate AD diagnoses; #For moderate-to-severe AD diagnoses; ♮Determined post-hoc as data was derived from bulk RNAseq; Pre-treated, simultaneous treat, or treated after establishing the model/system paradigm; ↑, increase; ↓, decrease; ≈, no change; ACh, acetylcholine; AChE (*AChE)*, acetylcholinesterase; AD, Alzheimer's disease; APP/PS1, APP Swedish mutation/presenilin 1; APPswe, APP Swedish mutation; BDNF, brain-derived neurotrophic factor; BMP-4, bone morphogenic protein 4; BuChE, butyrylcholinesterase; CCL20, chemokine ligand 20; ChAT, choline acetyltransferase; CXCL10, C-X-C motif chemokine 10; FAD, familial Alzheimer's disease; GDNF, glial cell-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GLT, glutamate transporter; IBA1, ionized calcium binding adaptor molecule 1; IGF-1, insulin-like growth factor 1; IL, interleukin; IFNγ, interferon gamma; LPS, lipopolysaccharide; NGF, nerve growth factor; NMDAR, *N*-methyl-D-aspartate receptor; TNFα, tumour necrosis factor alpha.

Drug Class	Drug Name	Mechanism of Action	Direct Effect	Indirect Effect
Acetylcholinesterase inhibitors*	Donepezil	A reversible cholinesterase inhibitor that functions through both competitive and non-competitive mechanisms; Allosterically modulates enzyme activity; Only inhibits AChE (Francis, Palmer et al., 1999; Lanctôt, Herrmann et al., 2003; McGleenon, Dynan et al., 1999)	↓ intracellular Ca^{2+} (Makitani, Nakagawa et al., 2017) ↓ reactive oxygen species (Makitani, Nakagawa et al., 2017)	
	Galantamine	A cholinesterase inhibitor that modulates nicotinic receptors through allosteric interactions (Lanctôt, Herrmann et al., 2003; Wu, Zhao et al., 2015)	↓ morphological changes (Wu, Zhao et al., 2015) ↓ / ≈ GFAP (Unger, Svedberg et al., 2006; Wu, Zhao et al., 2015) ↓ TNFα, IL-6 (Wu, Zhao et al., 2015)	
	Rivastigmine	A pseudo-irreversible cholinesterase inhibitor; Once cleaved by AChE, the enzyme becomes covalently modified, thereby preventing ACh hydrolysis for several hours even once this chemical is eliminated from the plasma (Francis, Palmer et al., 1999; McGleenon, Dynan et al., 1999); Inhibits both AChE and BuChE (Lanctôt, Herrmann et al., 2003)	↓ GFAP (Mohamed, Keller et al., 2016)	
	Other AChEI (Metrifonate)	An irreversible cholinesterase inhibitor	↑ NGF, BDNF (Mele & Juric, 2014)	
	ACh receptor		↑ GDNF (Liu, Zeng et al., 2015) ↓ oxidative stress-induced apoptosis	↓ IBA1 in microglia (Liu, Zeng et al., 2015)

	agonist		(Liu, Zeng et al., 2015) ↓ GFAP (Liu, Zeng et al., 2015) ↓ Caspase-9 (Liu, Zeng et al., 2015) ↓ IL-6, TNFα, IL-1β, IL-8, IL-13 (Revathikumar, Bergqvist et al., 2016) ↓ BuChE (Revathikumar, Bergqvist et al., 2016) ≈ IFNγ, IL-2, IL-44, IL-10, IL-12p70 (Revathikumar, Bergqvist et al., 2016) ↓ NF-κB pathway (Patel, McIntire et al., 2017)	↑ anti-inflammatory/ neuroprotective effects in microglia (Revathikumar, Bergqvist et al., 2016)
NMDAR antagonist[#]	Memantine	An uncompetitive antagonist that preferentially binds to NMDAR after excessive glutamate activation, thereby allowing normal levels of glutamate-based synaptic transmission to occur without inhibition (Reisberg, Doody et al., 2003)	≈ GFAP (Unger, Svedberg et al., 2006) ↓ CCL20, CXCL10, BMP-4 (Suhs, Gudi et al., 2016) ↑ IGF-1 (Suhs, Gudi et al., 2016) ↓ intracellular Ca^{2+} (Lee, Ting et al., 2010)	
	Other NMDAR antagonist (Riluzole)		↑ GLT-1 (Carbone, Duty et al., 2012) ↑ glutamate uptake (Carbone, Duty et al., 2012; Yoshizumi, Eisenach et al., 2012) ↑ NGF, BDNF, GDNF (Mizuta, Ohta et al., 2001) ≈ /↓ Modest return to baseline levels of astrocyte-specific transcripts♮ (Okamoto, Gray et al., 2018) ↑ intracellular Ca^{2+} stores (Yoshizumi, Eisenach et al., 2012) ↑ glutamate release? (Yoshizumi, Eisenach et al., 2012)	↓ Modest return to baseline levels of microglia-specific transcripts (especially DAM profiles)♮ (Okamoto, Gray et al., 2018)

Rodent and human models used to investigate AD function:

Species	Technique	Model	Age	Brain Area Assessed	Citation
Mouse	Dissociated culture	C57BL/6 black treated with 500 μM H_2O_2	Neonate	Midbrain	(Liu, Zeng et al., 2015)
		ICR	Neonate	Whole brain	(Mizuta, Ohta et al., 2001)
		C57BL/6 black stimulated with 60 ng/mL LPS	Neonate	Cortex	(Patel, McIntire et al., 2017)
		E15/E16 Swiss cultured without growth factors for 3 day	Embryonic	Midbrain	(Carbone, Duty et al., 2012)
		ChAT promoter transgenic	1 month	Hippocampus	(Pabst, Braganza et al., 2016)
		5X FAD	6 month	Cortex Hippocampus	(Okamoto, Gray et al., 2018)
	Brain slice and/or sectioning	C57BL/6 black	Unspecified	Hippocampus	(Navarrete, Perea et al., 2012)
		ChAT promoter transgenic	1 month	Hippocampus	(Pabst, Braganza et al., 2016)
		APPswe transgenic	8 month	Hippocampus	(Mohamed, Keller et al., 2016)
			10 month	Cortex	(Unger, Svedberg et al., 2006)
	In vivo	ChAT promoter transgenic	7-10 week	Hippocampus	(Pabst, Braganza et al., 2016)
		APP/PS1	10 month	Hippocampus	(Wu, Zhao et al., 2015)
Rat	Dissociated astrocyte culture	Wistar Hannover	Neonate	Cortex	(Mele & Juric, 2014; Yoshizumi, Eisenach et al., 2012)
		Wistar Hannover treated with 1 μM bradykinin	Neonate	Cortex	(Makitani, Nakagawa et al., 2017)
	Dissociated culture	Wistar Hannover treated with 100 ng/mL LPS or 100 ng/mL TNFα	Neonate	Cerebrum	(Suhs, Gudi et al., 2016)
	Brain slice and/or sectioning	Wistar Hannover	3-4 month	Hippocampus	(Navarrete, Perea et al., 2012)
Human	Dissociated astrocyte culture	IL-1β stimulated	Foetal	Unspecified	(Revathikumar, Bergqvist et al., 2016)
		500 μM glutamate and/or 500 nM QUIN stimulated	Foetal	Cerebrum	(Lee, Ting et al., 2010)
		500 μM glutamate and/or 500 nM QUIN stimulated	Adult	Cerebrum	(Lee, Ting et al., 2010)
	Brain slice and/or sectioning	Autopsy	Adult	Cortex, Hippocampus	(Teaktong, Graham et al., 2003)

Overview of drug treatments tested in pre-clinical setting:

Reagent	Concentration	Duration of Treatment	Citation
Donepezil	10 μM	24 hours	(Makitani, Nakagawa et al., 2017)
Galantamine	2 mg/kg	10 day	(Unger, Svedberg et al., 2006)
	5 mg/kg	8 weeks, 2X per day	(Wu, Zhao et al., 2015)
Rivastigmine	0.3 mg/kg	8 weeks	(Mohamed, Keller et al., 2016)
Other AChEI (Metrifonate)	1 nM-100 μM; maximum effect at 10 μM	24 hours	(Mele & Juric, 2014)
ACh receptor agonist (Nicotine)	1 μM		(Revathikumar, Bergqvist et al., 2016)
	10 μM	24 hours	(Liu, Zeng et al., 2015; Revathikumar, Bergqvist et al., 2016)
	100 μM		(Revathikumar, Bergqvist et al., 2016)
ACh receptor agonist (GTS21)	30 μM	1 hour	(Patel, McIntire et al., 2017)
ACh receptor stimulation (electric pulse; optogenetics)			(Navarrete, Perea et al., 2012; Pabst, Braganza et al., 2016)
Memantine	20 μM	5 minutes	(Lee, Ting et al., 2010)
	0.1-100 μM	12-24 hours	(Suhs, Gudi et al., 2016)
	10 mg/kg	10 days	(Unger, Svedberg et al., 2006)
Other NMDAR antagonist (Riluzole)	1 μM	5 minutes	(Yoshizumi, Eisenach et al., 2012)
	100 μM	3 days	(Carbone, Duty et al., 2012)
	426 μM	24 hours	(Mizuta, Ohta et al., 2001)
	13 mg/kg	5 months	(Okamoto, Gray et al., 2018)

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