UNIVERSITA' DEGLI STUDI DI TORINO
DIPARTIMENTO DI NEUROSCIENZE

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Terapia con GLP1-agonisti: nuovi orizzonti di utilizzo nelle patologie neurologiche degenerative in pazienti diabetici e non

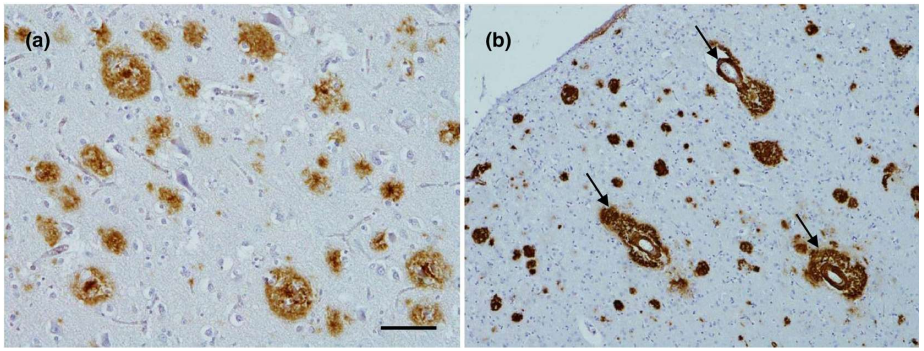
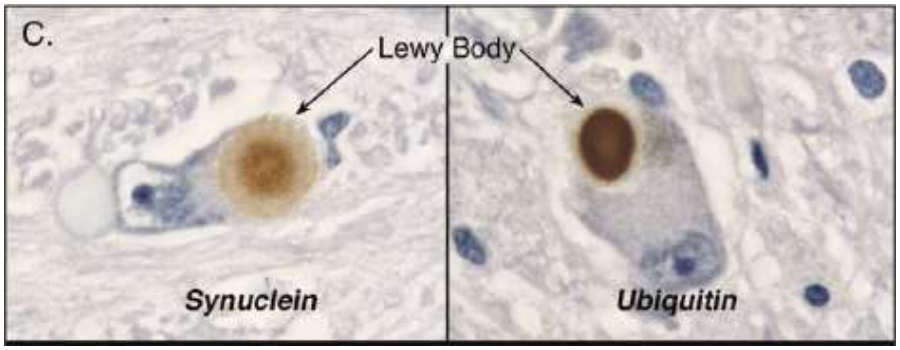
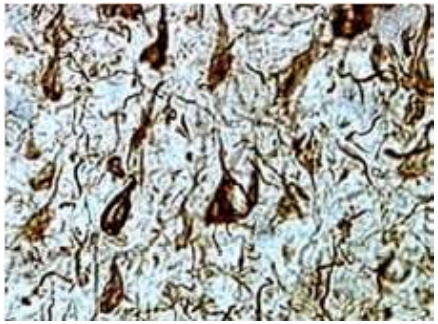
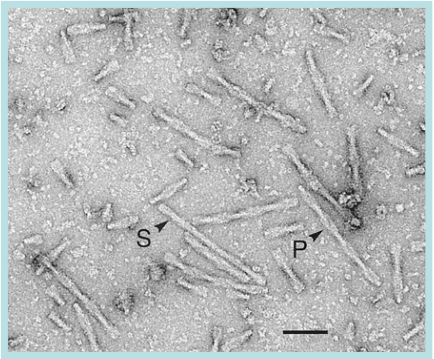
Torino 18 Settembre 2023

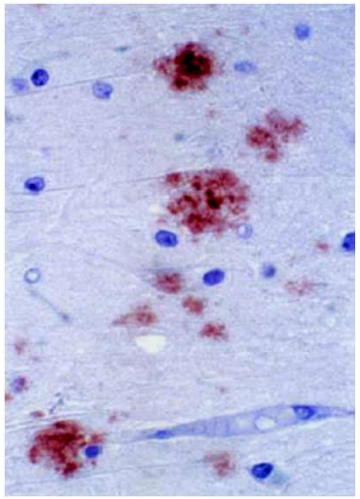
Sharing experience in Diabetologia ed Endocrinologia

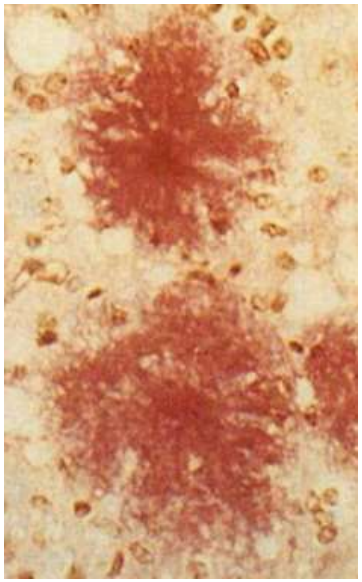
ISTITUTO AUXOLOGICO ITALIANO
IRCCS OSP. S. GIUSEPPE , PIANCAVALLO (VB)

Malattie neurodegenerative

- Patologie del sistema nervoso caratterizzate da:
  - Processo degenerativo progressivo di uno o più sistemi neuronali
  - Assenza di infiammazione e necrosi tissutale

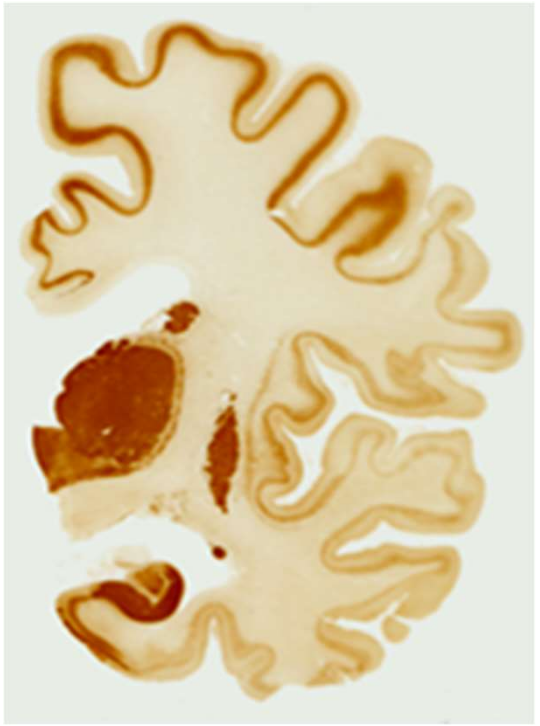
β Amiloide		M. di Alzheimer *(50 milioni di casi)*
α synucleina		M. di Parkinson *(6.1 milioni di casi)* DLB MSA Hallervorden-Spatz
P. tau iperfosforilata	 	M. di Alzheimer FTLD PSP D. Corticobasale





type 1 PrP^{res}
MM 129

type 2 PrP^{res}
VV 129



Diabete e Malattie neurodegenerative (M di Parkinson)

Study design	Sample size	Results	Diabetes and PD association	References
Retrospective study	200 IPD patients and 200 controls	The cumulative incidence of ischemic stroke, myocardial infarction, and diabetes mellitus was higher in control than in PD patients	22 controls and 13 cases with diabetes	[147]
Retro prospective, case control study	119 presumptive etiology of IPD and 238 controls	The cumulative incidence of ischemic stroke, hypertension, and diabetes mellitus (DM) was not significantly different between control and PD patients	Diabetes more prevalent among controls	[148]
Cohort study	791 PD patients out of total 24,831 patients reported Parkinsonism whereas remaining 24,040 patients did not report any symptoms	Rates of diabetes among the population with Parkinsonism were higher than expected	29.7% of PD patients and 21.5% of controls had DM	[149]
Cohort study	15,306 PD patients; 30,612 controls	The occurrence of diabetes, ischemic heart disease, and myocardial infarction was more common in persons with Parkinsonism compared to those without Parkinsonism	PD patients and controls showed similar admission rates for diabetes	[150]
Case control study	352 IPD patients; 484 individuals without PD	Risk of PD was reduced in case of female and male smokers with and without diabetes	Diabetes prevalence in 7.4% of PD patients and 12.6% in controls	[151]
Population-based cross-sectional study	197 PD patients and 197 controls	PD cases did not differ significantly from referent subjects with respect to proportion with diagnosis of diabetes, ischemic heart disease, and myocardial infarction	PD patients did not show significant comorbidities	[152]
Hospital series case control study	178 PD patients and 533 individuals with other neurological diseases	Diabetes, high blood pressure, high blood glucose, high blood cholesterol, and triglycerides were significantly less frequent in IPD than in controls	3.4% of PD patients and 10.9% of controls had DM	[153]
Prospective, cohort study	51,552 individuals with 633 PD diagnosis	T2DM is linked to a higher risk for the development of PD	T2DM is associated with increased PD	[154]
Longitudinal, cohort study	1,030 PD patients	Diabetes was associated with parkinsonian signs, especially gait disturbance, postural reflex impairment, and vascular factors, that play a key role in this association	Diabetes is associated with more severe PD	[155]
Meta-analysis	NA	A significant upregulation of substantia nigra genes in PD, which have biological association with diabetes, cancer, and inflammation	Shared dysregulated pathways between T2DM and PD	[156]
Prospective, cohort study	556 patients with PD	Men with diabetes have a higher risk of developing PD than non-diabetic men	T2DM is associated with an increased risk of PD in men	[157]
Case control study	318 PD patients and controls	Preceding a diabetic condition increases the risk for the onset of PD	Diabetes preceding PD onset	[158]
Meta-analysis	NA	Diabetes is an important risk factor for PD	Diabetes could be risk factor for future PD	[5]
Genome-wide association studies	NA	Type 1 and 2 diabetic patients have deficits in cognitive functions	Shared molecular pathways between PD and T1DM	[159]
Cohort study	656 PD patients	No evidence of a relationship between DM and risk of developing PD	No association between PD and DM	[160]
Case control	1931 PD patients and 9651 controls	High risk of developing PD with T2DM	T2DM is associated with an increased risk of PD, especially early onset of PD	[161]
Prospective, cohort study	21611 diabetic patients and 267 051 controls	Diabetes could be a risk factor for future PD progression	T2DM is associated with an increased risk of PD	[11]
Case control	53 PD patients with dementia and 57 patients with PD	The prevalence of insulin resistance is significantly higher in PD-associated dementia as compared to those nondemented PD	Insulin resistance is associated with an increased risk of dementia in PD	[26]
Case–control	89 patients with diabetes and 89 controls	Onset of diabetes before the onset of PD is a high-risk factor for more severe PD symptoms	T2DM is associated with increased PD severity	[19]
Case–control	603,413 PD patients and 472 718 Controls	Diabetic patients showed a significantly increased risk of PD compared to the control subjects	Diabetes is associated with increased risk of PD	[162]
Case–control	64,166 diabetic patients and 698 587 controls	Increased incidence of PD risk in T2DM by 2.2-fold	T2DM is associated with increased risk of PD	[163]
Integrative network analysis	NA	Mitogen-activated protein kinase (MAPK) cascade, serine-threonine kinase activity, activation of the immune response, insulin receptor, and lipid signaling are convergent pathways between TDM and PD	Convergent molecular pathways between T2DM and PD	[164]
System-based approach	NA	T2DM and PD pathophysiology are strongly linked to each other	A positive association between T2DM and PD	[165]
Case–control	NA	The association between diabetes and postural instability and gait difficulty persisted after controlling for comorbid hypertension and body mass index	Diabetes is associated with severe postural instability and gait difficulty in PD	[166]
Meta-analysis	1,761,632 individuals	Individuals with diabetes had higher incidence of PD compared to non-diabetic individuals	Diabetes is associated with a 38% increased risk of PD	[16]
Retro prospective, case–control	36,294 diabetic patients and 108,882 healthy controls	Increased risk of PD with patients having DM compared to non-DM patients	DM increased the risk of PD by 23%	[4]
A record-linkage cohort study	2,017,115 T2DM patients and 6,173,208 reference cohort	There were significantly increased rates of PD following T2DM	T2DM was relatively higher in patients with PD	[167]
Population-based case study	25 patients with PD and DM 25 PD patients without diabetes	DM was associated with higher tau (cerebrospinal fluid) CSF level, lower striatal dopamine (DA) transporter binding, and higher motor score in patients with PD	PD with DM was associated with severe motor progression or cognitive decline	[10]
Retrospective observational cohort study	NA	Antidiabetic drug thiazolidinediones reduced risk of developing PD in the diabetic patients	Treatment of diabetes decreased PD progression by 30%	[168]
Cohort study	33,443 individuals with PD	DM and being underweight were associated with increased incidence of PD	Significant interaction between diabetes and PD development	[169]

Diabete e Malattie neurodegenerative
(M di Alzheimer e M di Parkinson)

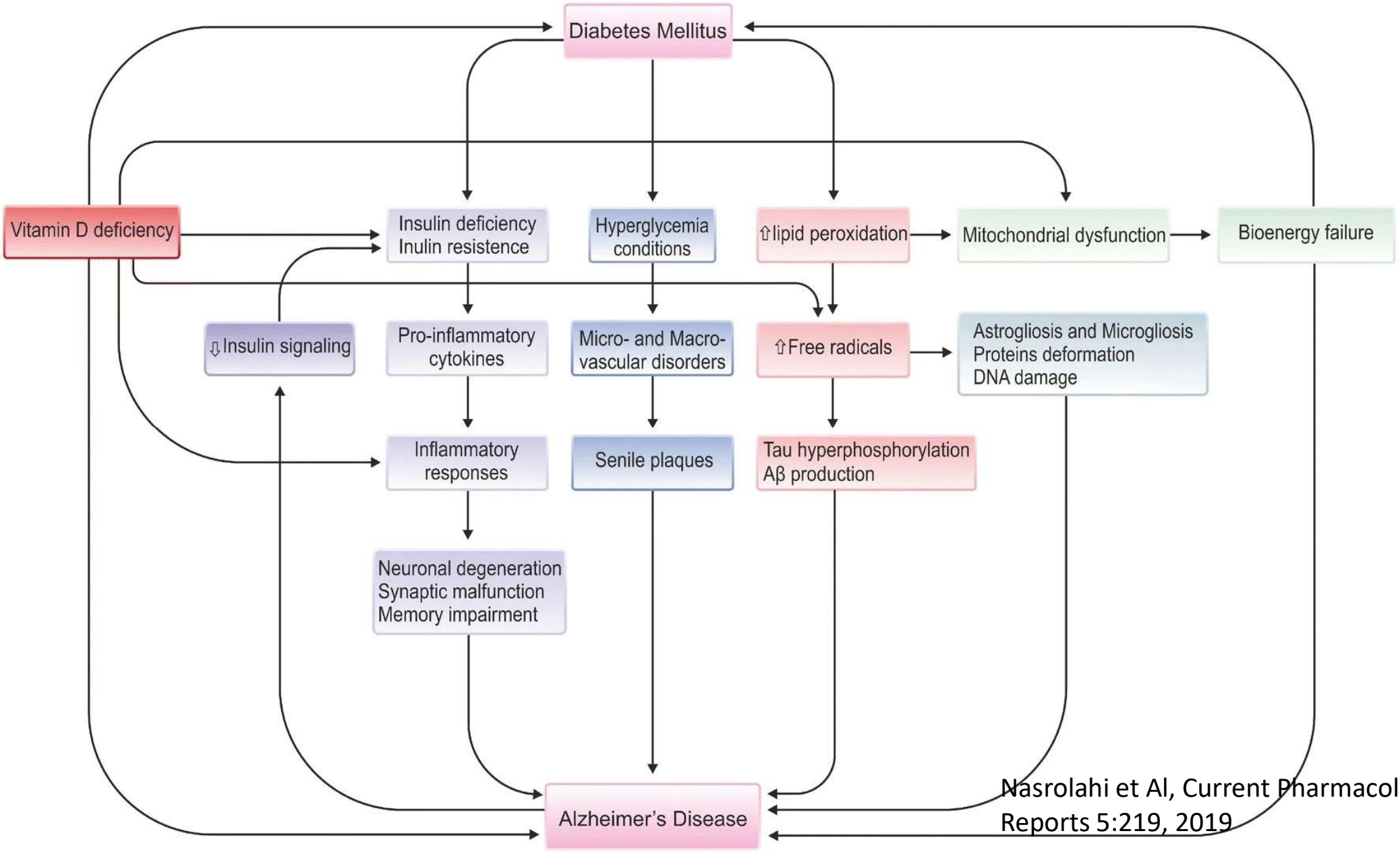
Comorbidità fra MA e DM superiore all'attesa di 1.3 - 1.9 volte

I pazienti affetti da DM hanno una probabilità maggior di sviluppare decadimento cognitivo

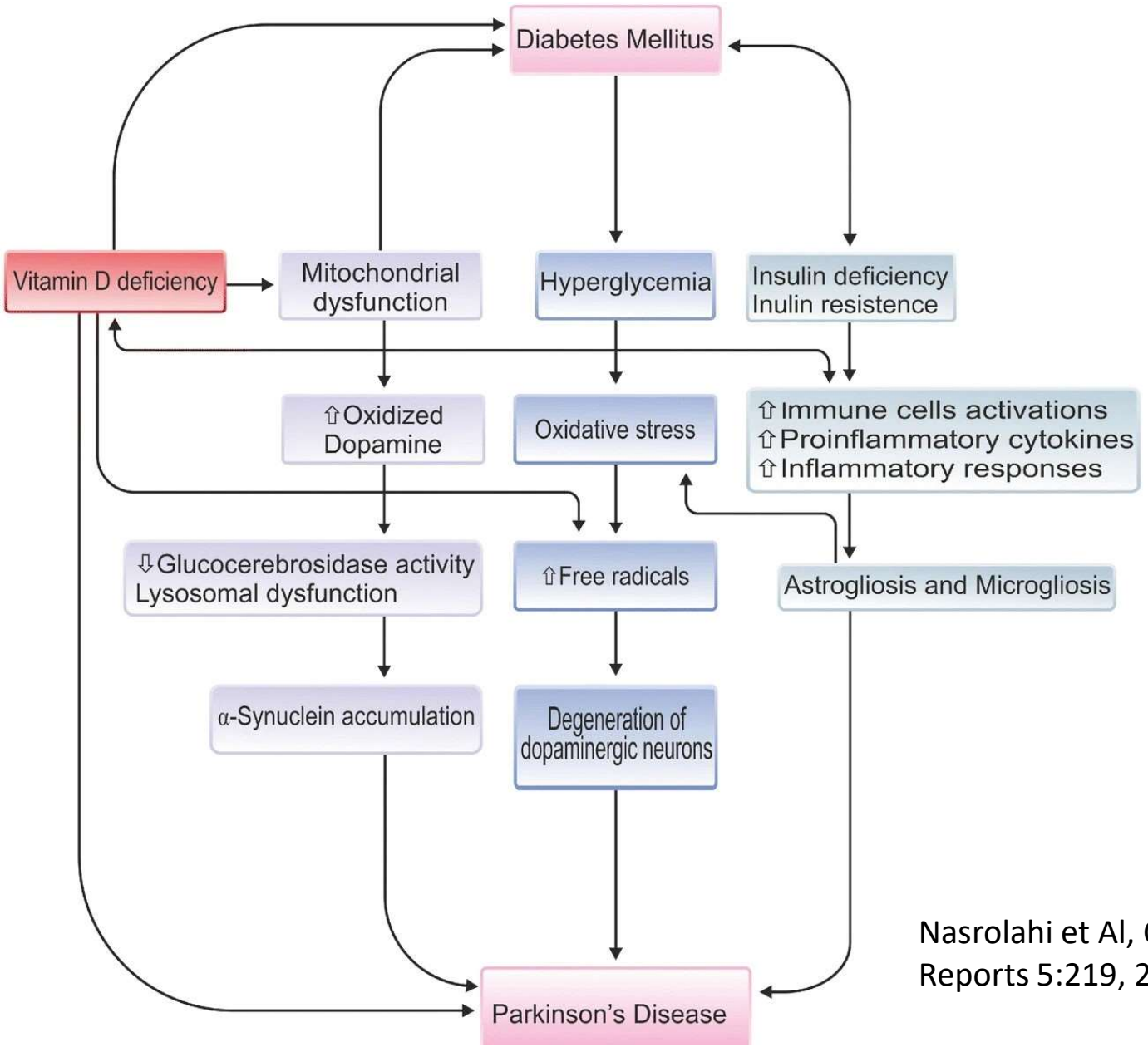
Studi di coorte suggeriscono un aumento del rischio di sviluppare MP nei soggetti con DM
Studi caso-controllo non confermano l'aumento del rischio

La presenza di DM rende la MP più grave e ne rende più rapida la progressione

Ridotta incidenza di MP in pazienti con DM trattati con inibitori della dipeptidil-peptidasi-4 o tiazolidinedioni



Nasrolahi et Al, Current Pharmacology Reports 5:219, 2019



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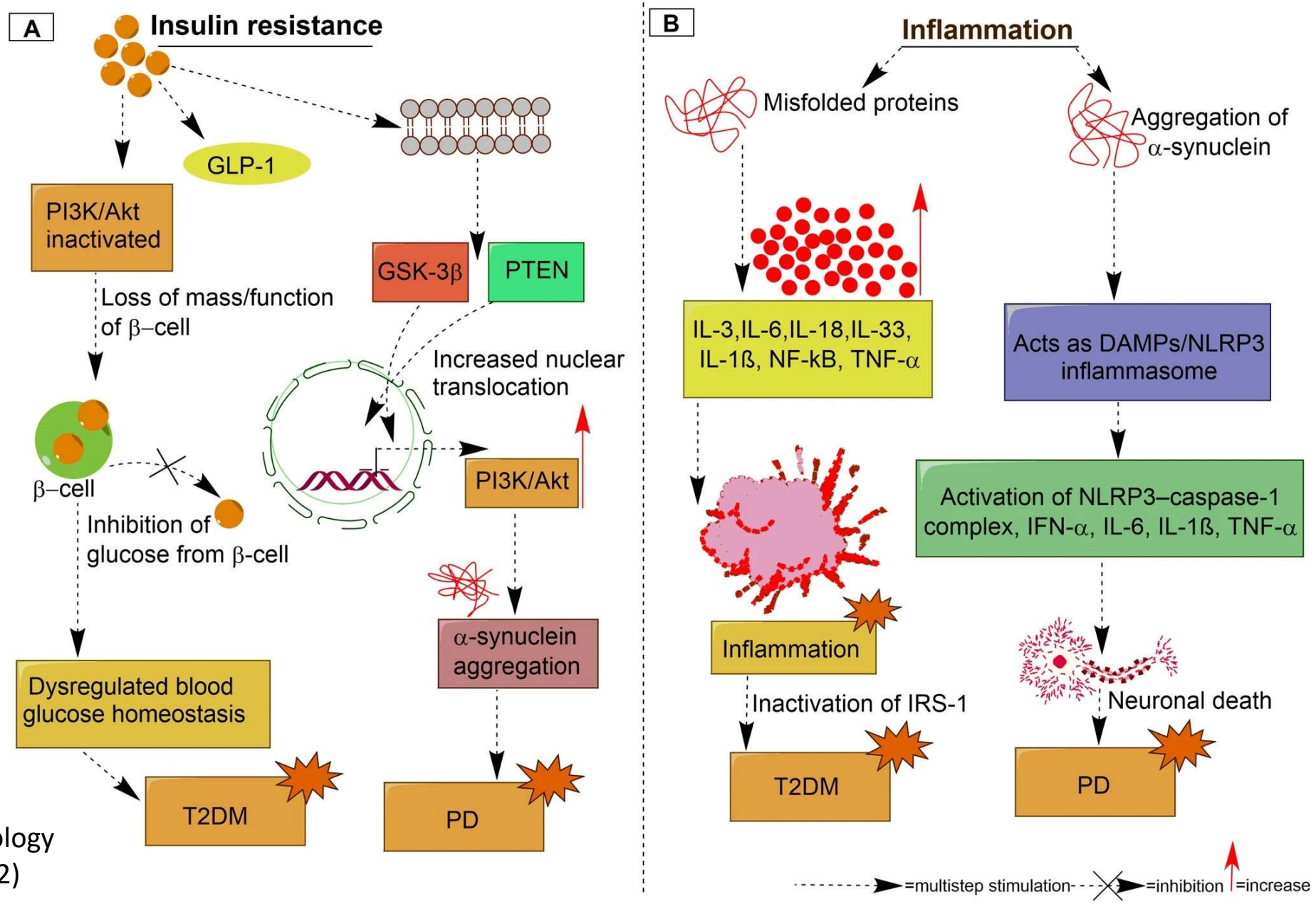
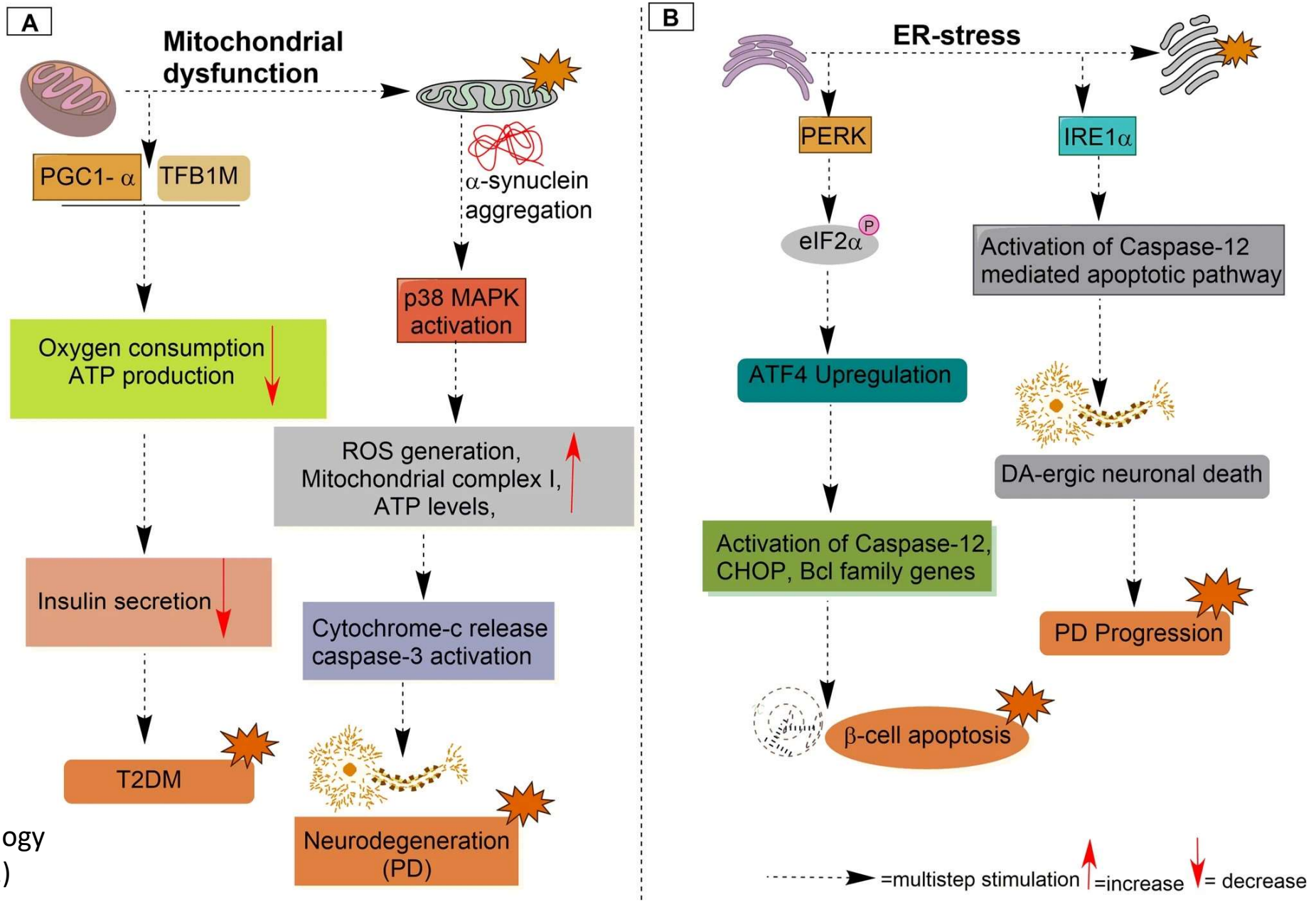


Molecular Neurobiology
59:4466–4487 (2022)



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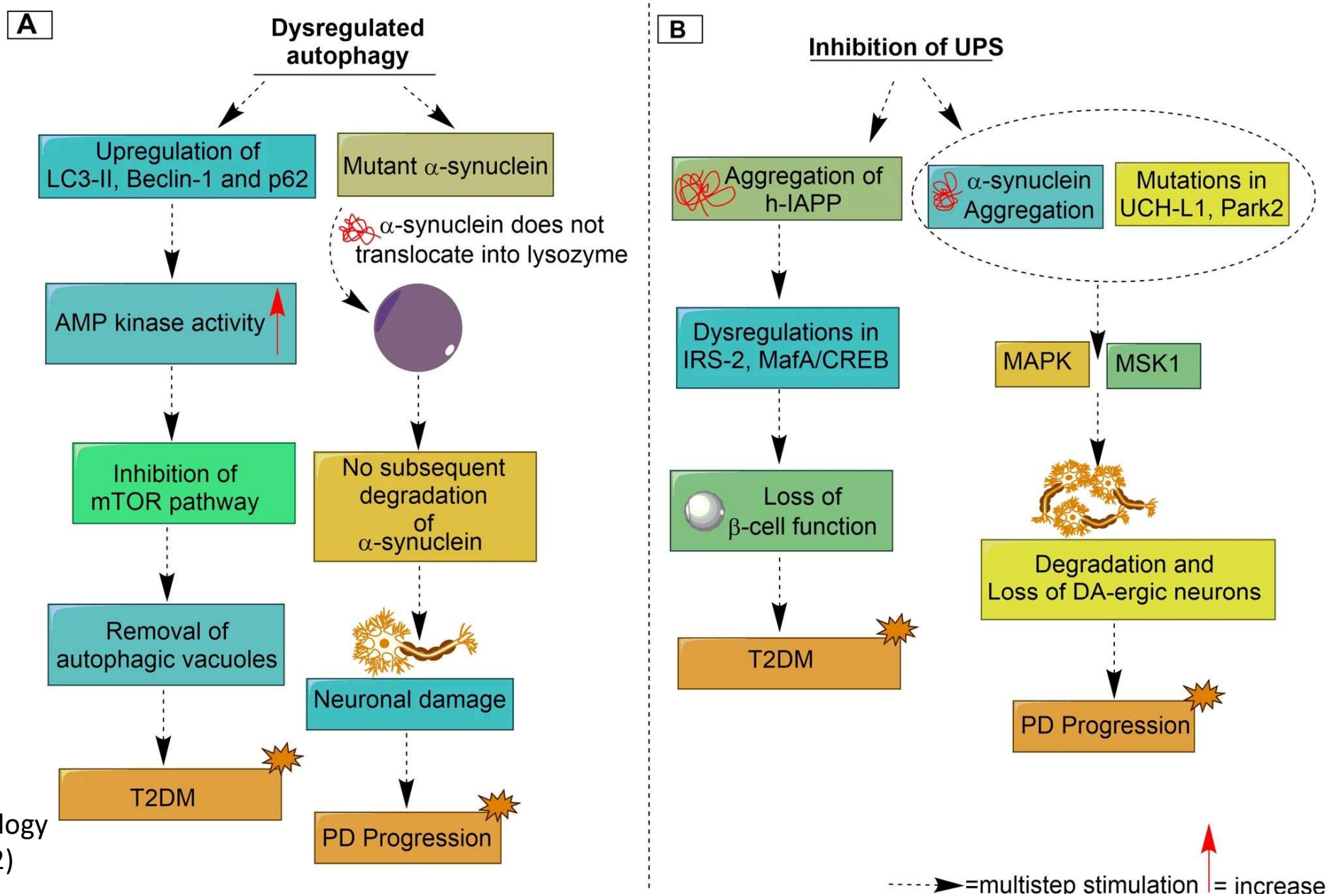
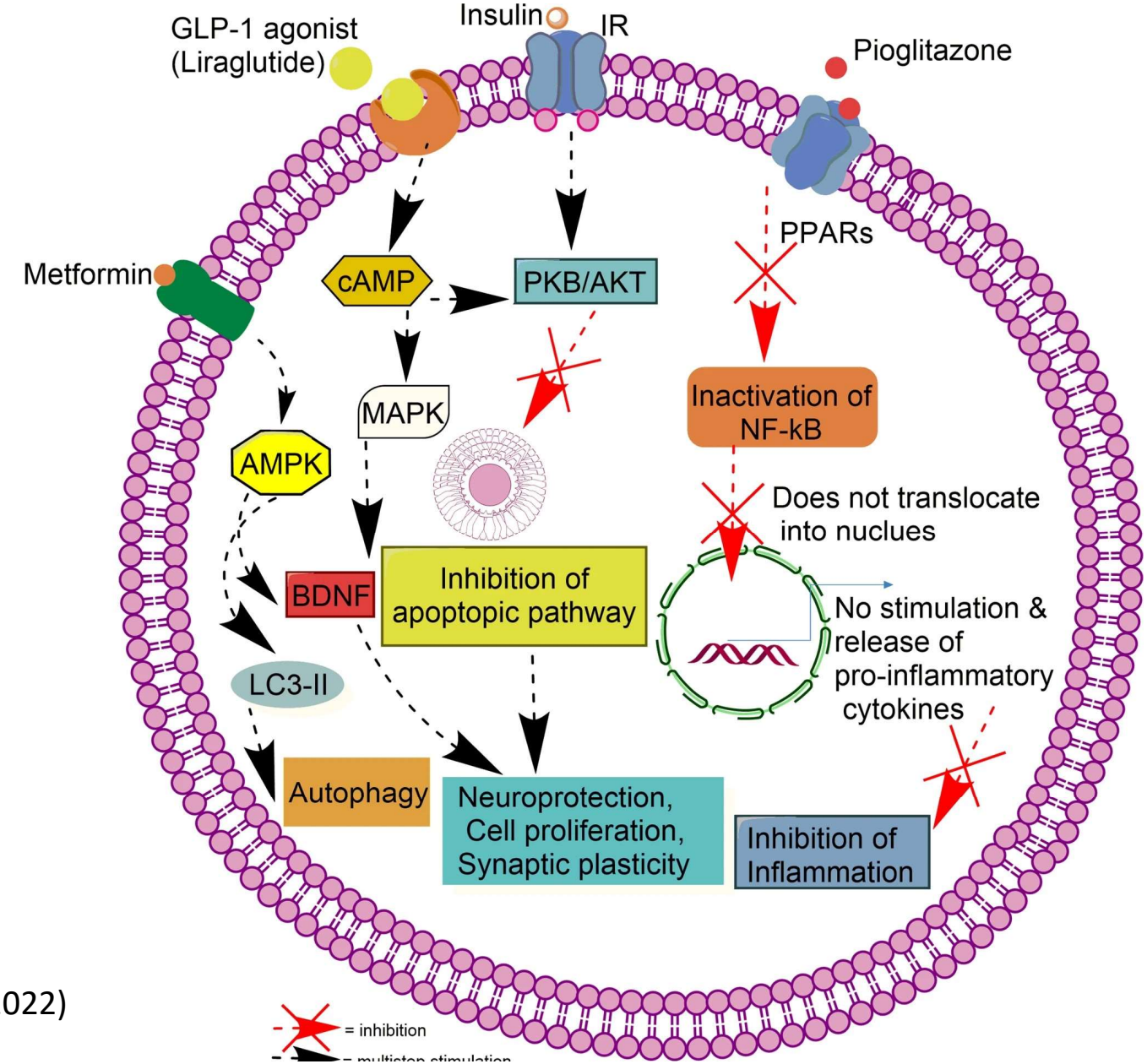


Molecular Neurobiology
59:4466–4487 (2022)

Possibili meccanismi terapeutici di farmaci antidiabetici nei confronti della M di Parkinson



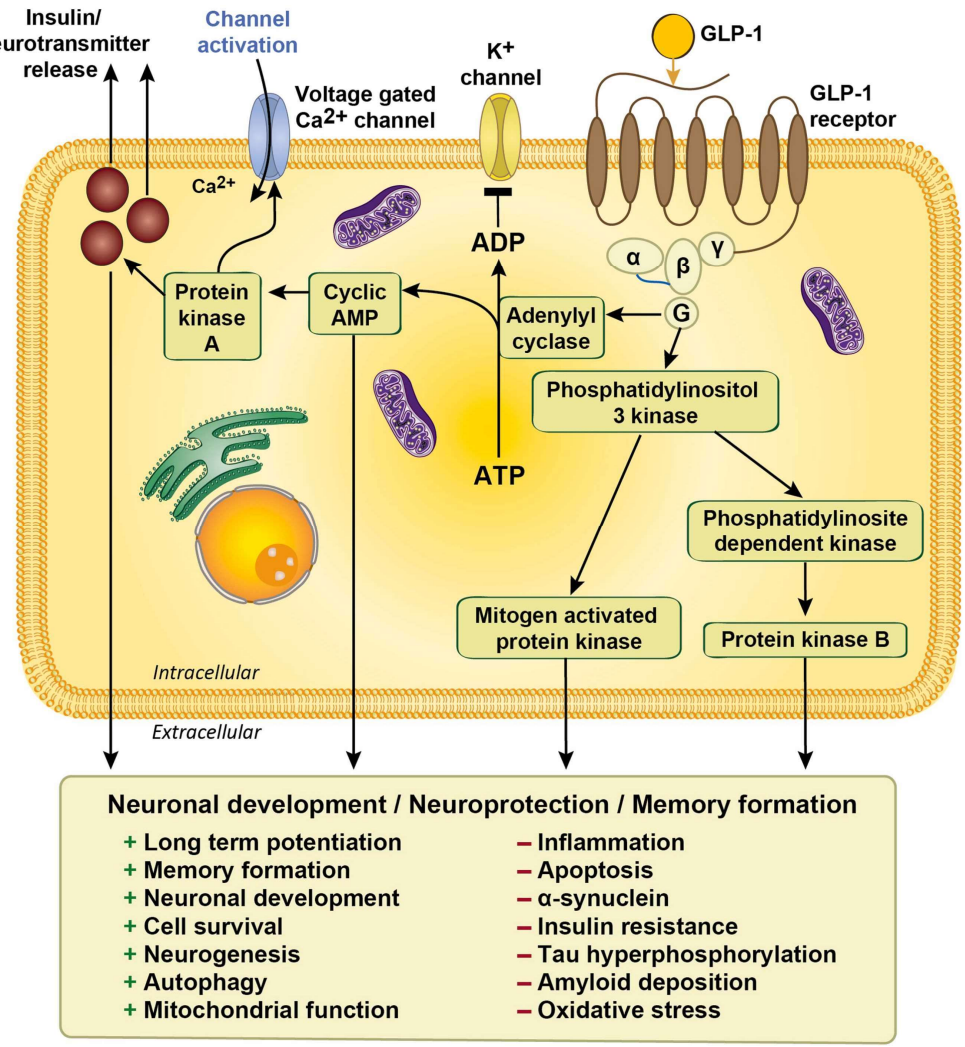
Molecular Neurobiology 59:4466–4487 (2022)

GLP-1 (Glucagon Like Peptide 1) è secreto da popolazioni cellulari del tratto gastrointestinale, ma anche da alcune popolazioni neuronali nel nucleo del tratto solitario.

Recettori per GLP-1 e/o GLP-1 sono stati identificati nel talamo, ipotalamo, neuroni piramidali dell'ippocampo, corteccia, cellule di Purkinje e nel tronco, nonché in astrociti e microglia.

Il signaling di GLP-1 è implicato anche nelle funzioni cognitive (miglioramento di apprendimento e memoria in ratti che sovraesprimono i recettori GLP-1 nell'ippocampo)

GLP-1 signaling nel cervello e cascate di eventi potenzialmente favorevoli



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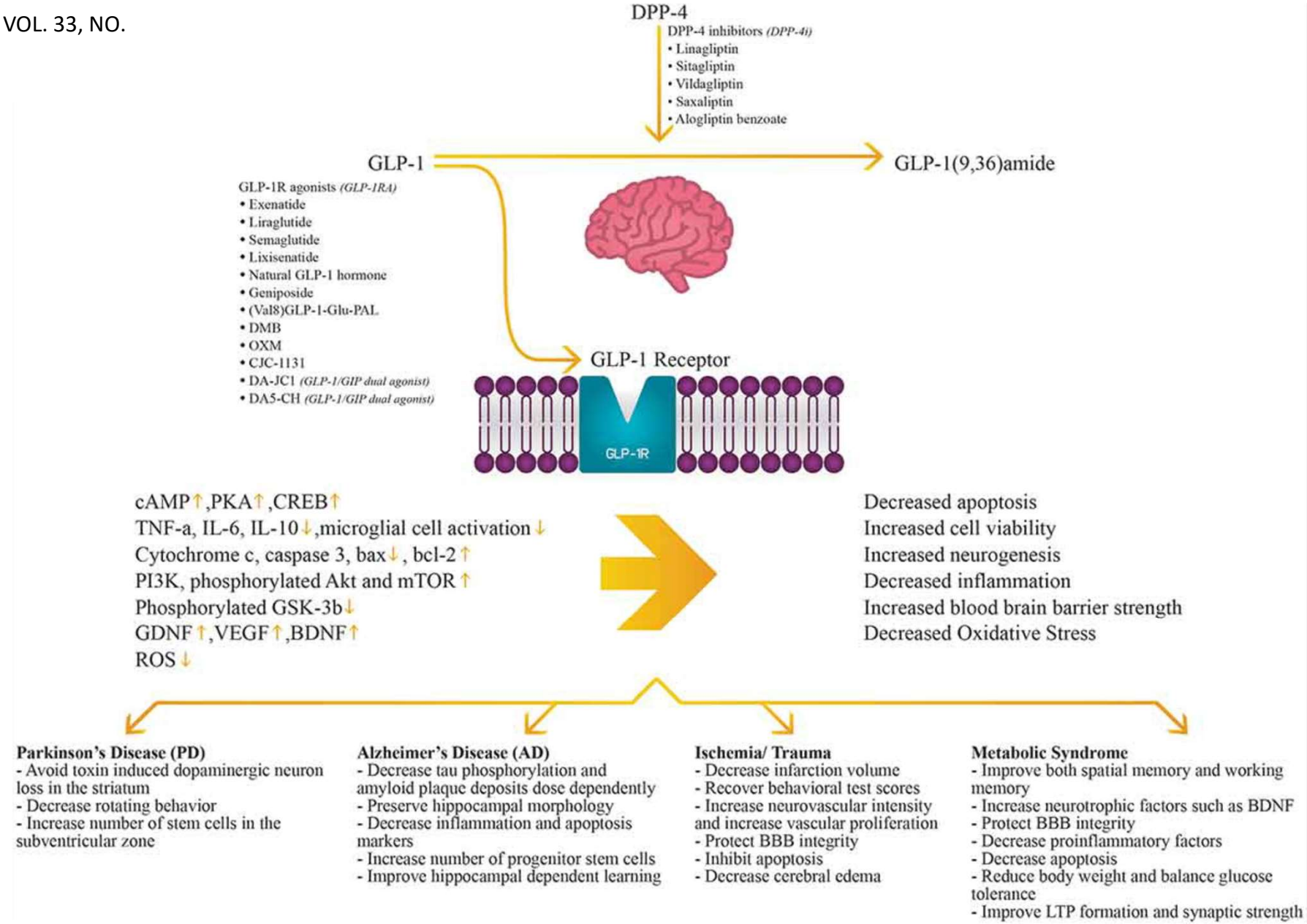

Studies	Experiment	GLP-1RA	Observations	Publications
Preclinical studies	***Animal model***			
AD features				
Plaque load	APP/PS1/tau mice	Liraglutide	Reduction of plaque load	[72,76,77]
	5xFAD mice	Liraglutide	Reduction of plaque load	[78]
	APP/PS1 mice	Lixisenatide	Reduction of plaque load	[76]
	3xTg-AD mice	Exendin-4	Reduction of plaque load	[62]
Tau phosphorylation	APP/PS1/tau mice	Liraglutide	Reduction of neurofibrillary tangles	[56,72]
	hTauP301L mice	Liraglutide	Reduced Tau phosphorylation	[58]
	Aβ injection in mice	Liraglutide	Reduced Tau phosphorylation	[67]
	APP/PS1 x db/db mice	Liraglutide	Reduced Tau phosphorylation	[79]
	Streptozotocin injection in mice	Dulaglutide	Reduced Tau phosphorylation	[73]
Cognitive and memory performance	Aβ injection in mice	Liraglutide	Improved cognitive impairment	[74]
	Aβ injection in rats	Lixisenatide	Improved spatial memory	[80]
	Streptozotocin injection in mice	Dulaglutide	Improved memory ability	[73]
Other	Aβ injection in non-human primates	Liraglutide	Reduced synaptic loss	[74]

Studies	Experiment	GLP-1RA	Observations	Publications
Preclinical studies	***Animal model***			
PD features				
Dopaminergic neuronal loss	6-OHDA rat model	Liraglutide	No influence on dopaminergic neuronal loss	[59]
	6-OHDA rat model	Exendin-4		[55]
	6-OHDA rat model	Exendin-4′	Neurogenesis Reduced lesions	[60]
Motor performance	MPTP mouse model	Liraglutide	Improved motor control	[64]
	MPTP mouse model	Lixisenatide	Improved motor control	[64]
α-synuclein aggregation	Preformed fibrils injection in striatum of human A53T α-synuclein mice	Exendin-4 (NLY01)	Reduced loss of dopaminergic neurons and improved motor performance	[81] [82]
	Preformed fibrils injection in the olfactory bulb of C57BL/6J mice	Exendin-4	No significant reduction of α-synuclein aggregation	

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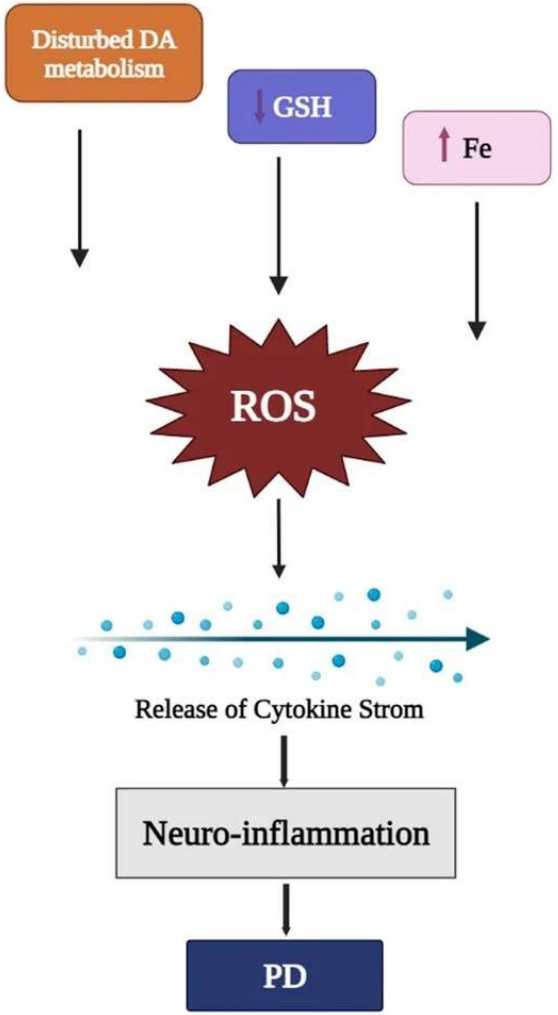
Mechanism of the neuroprotective effect of GLP-1 in a rat model of Parkinson's with pre-existing diabetes

Eman A. Elbassuoni[a,*], Rasha F. Ahmed[b]



Studies	Experiment	GLP-1RA	Observations	Publications
Clinical trials	*Trial ID*			
AD	NCT02140983	Liraglutide	Increased connectivity in the default mode network	[85]
	NCT01469351	Liraglutide	Improved cerebral glucose uptake	[86,87]
	NCT01843075	Liraglutide	Improved cognition	[88]
	NCT01255163	Exenatide	No significant changes in cognition	[89]
	NCT04777396	Semaglutide	Recruiting	
	NCT04777409	Semaglutide	Recruiting	
PD	NCT01971242	Exenatide	Improved motor and cognitive outcomes	[90]
	NCT01174810	Exenatide	Improved motor and cognitive outcomes	[91]
	NCT02953665	Liraglutide	Active	
	NCT03439943	Lixisenatide	Active	
	NCT04154072	Exenatide	Active	
	NCT03659682	Semaglutide	Not yet recruiting	

	Target /Drug name	Number of patients	Trial duration	Dosage	Outcomes
AD					
Gejl et al. (2016)	GLP-1 analog, liraglutide	38 patients with AD (N = 18 treatment, 20 placebo)	26 weeks	1.8 mg daily	Prevented decline in cerebral glucose metabolism No cognitive benefit (not powered to see cognitive change)
Watson et al. (2019)	GLP-1 analog, liraglutide	26 mid-aged participants with subjective cognitive complaints (N = 15 treatment, 11 placebo)	12 weeks	1.8 mg daily	Improved default mode network intrinsic connectivity No cognitive benefit (not powered to see cognitive change)
Mullins et al. (2019)	GLP-1 analog, exenatide	27 patients with probable AD (N = 13 Treatment, 14 placebo)	18 months	5 mcg twice daily	No cognitive benefit (not powered to see cognitive change)
PD					
Aviles-Olmos et al. (2013)	GLP-1 analogue, exenatide	45 patients with moderate PD (N = 21 treatment, 24 control)	12 months	5-μg twice daily	Treatment improved motor and cognitive outcomes
Athauda et al. (2017)	GLP-1 analogue, exenatide	62 patients with moderate PD (N = 32 treatment, 30 placebo)	48 weeks	2 mg once weekly	Treatment improved motor outcomes No cognitive effects
Novak et al. (2019)	Insulin, Intranasal regular insulin	15 patients with a clinical diagnosis of PD or multiple system atrophy (N = 9 treatment, 6 placebo)	4 weeks	40 IU daily	Treatment improved motor performance and functionality

	Target /Drug name	Number of patients	Trial duration	Dosage	Outcomes
AD					
Claxton et al. (2015)	Insulin, Intranasal insulin detemir	60 patients with MCI or mild to moderate AD (N = 21 insulin detemir 20 IU, 19 insulin detemir 40 IU, 20 placebo)	3 weeks	20 or 40 IU daily	40 IU insulin detemir improved memory composite
Craft et al. (2012)	Insulin, Intranasal regular insulin	104 patients with amnestic MCI or mild to moderate AD (N = 30 placebo, 36 insulin 20 IU, 38 insulin 40 IU	4 months	10 or 20 IU twice-daily	10 IU (twice-daily) improved delayed memory Both doses preserved caregiver-rated functional ability
Craft et al. (2017)	Insulin, Intranasal regular insulin or insulin detemir	36 patients with MCI or mild to moderate AD (N = 12 regular insulin, 12 insulin detemir, 12 placebo)	4 months	40 IU daily	Regular insulin improved memory and preserved MRI volume
Craft et al. (2020)	Insulin, Intranasal regular insulin	240 patients with amnestic MCI or AD	12 months	40 IU daily	No cognitive or functional benefit
Luchsinger et al. (2016)	Metformin	80 participants with amnestic MCI (N = 40 treatment, 40 placebo)	12 months	1000 mg twice daily	Treatment improved recall of the Selective Reminding Test of verbal memory No other cognitive or biomarker benefits
Koenig et al. (2017)	Metformin	20 patients MCI or mild dementia due to AD	16 weeks (crossover design)	1000 mg twice daily	Treatment improved executive functioning
Sato et al. (2011)	PPAR-γ agonist, pioglitazone	42 patients with mild AD (N = 21 treatment, 21 placebo)	6 months	15–30 mg daily	Treatment improved cognition and regional cerebral blood flow in the parietal lobe
Watson et al. (2005)	PPAR-γ agonist, rosiglitazone	36 patients with amnestic MCI or probable AD (N = 24 treatment, 12 placebo)	6 months	4 mg daily	Treatment preserved delayed-memory and selective attention
Risner et al. (2006)	PPAR-γ agonist, rosiglitazone	499 patients with probable AD (N = 127 treatment 2 mg, 130 treatment 4 mg, 132 treatment 8 mg, 122 placebo)	24 weeks	2, 4 or 8 mg daily	No cognitive benefit (primary analysis) ApoE ε4 non-carriers may have cognitive and functional benefit (exploratory)
Chamberlain et al. (2020)	PPAR δ/γ dual agonist, T3D-959	34 patients with mild to moderate AD (N = 9 treatment 3 mg, 9 treatment 10 mg, 10 treatment 30 mg, 8 treatment 90 mg)	2 weeks	3, 10, 30, or 90 mg daily	Treatment improved cognition and cerebral glucose metabolism