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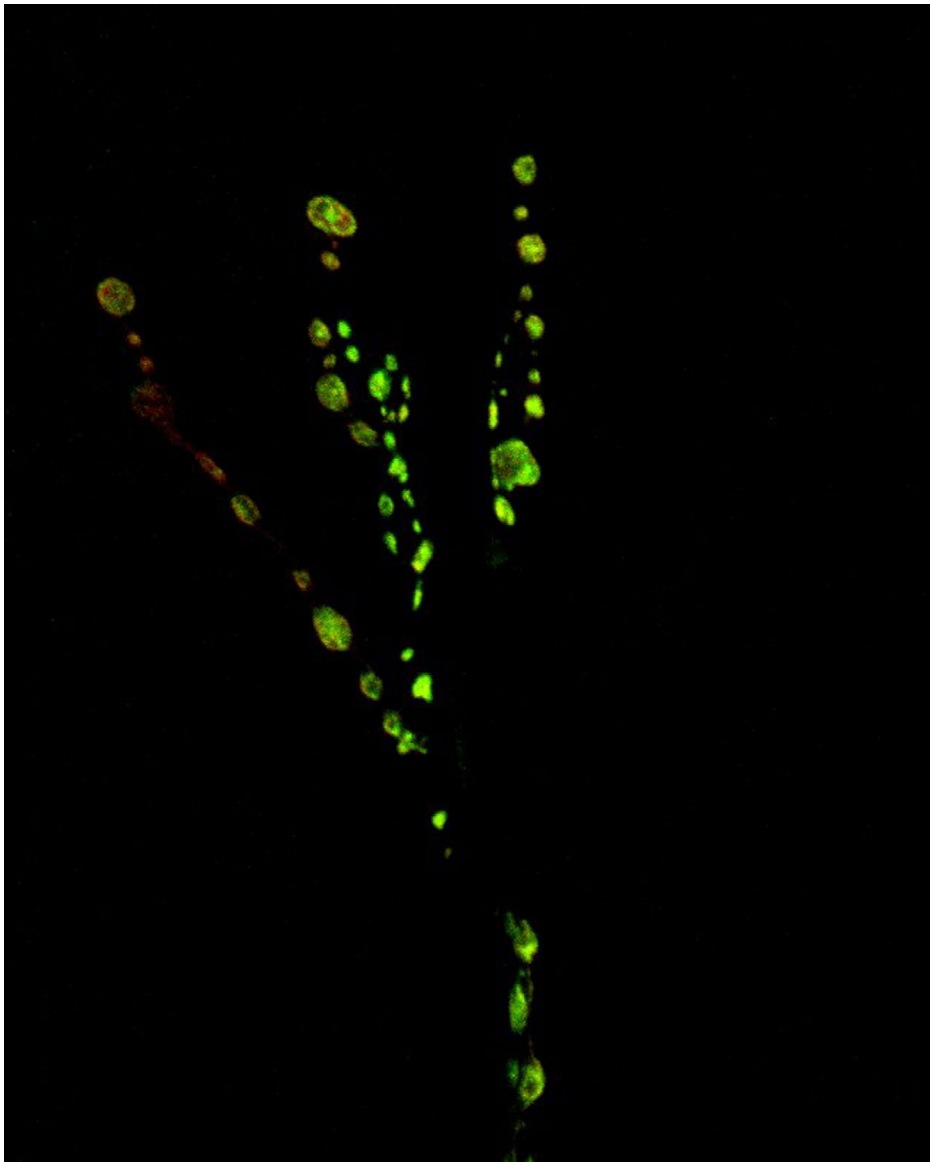

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NEUROSCIENCE | REVIEW ARTICLE

Synapses and α-synuclein signalling in disease

Carlo Breda[1], Flaviano Giorgini[1] and Joern R. Steinert[2*]

Abstract: Life expectancy is increasing worldwide, thus the incidence of neurodegenerative disorders (ND) such as Parkinson's (PD) and Alzheimer's (AD) diseases is on the rise. In the UK alone, ~700,000 people are suffering from these age-related disorders and this number is estimated to further increase by 2030, placing an enormous burden on healthcare. Several of these pathologies share the hallmark of protein misfolding, leading to neuronal dysfunction and ultimately cell death. Furthermore, a common characteristic of these disorders is the abnormal accumulation of protein aggregates/inclusions such as amyloid plaques and neurofibrillary tangles in AD and Lewy bodies in PD. Although the effect of accumulation of these insoluble proteins on molecular processes is still unclear, a view is emerging that compromised synaptic function may underlie the earliest symptoms of ND.

Subjects: Cell Biology; Neurobiology; Neuroscience

Keywords: α-synuclein; synapse; neurodegeneration; vesicle release; dopaminergic; Rab GTPases

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Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting ~1% of the retirement age population (de Rijk et al., 1995) and about 4% of the population over 80 years of age (de Lau & Breteler, 2006). The typical symptoms of this disease are motor disturbances (such as resting tremor and postural instability) and neuropsychiatric hallmarks including cognitive and behavioural dysfunctions. Pathologically, PD is characterised by the progressive loss of midbrain dopamine (DA)

ABOUT THE AUTHOR

The research group led by Joern R. Steinert is studying brain function with special interest in synaptic transmission and ion channel regulation predominantly under the involvement of nitric oxide signalling. The research interests concern neuronal function and dysfunction in neurodegeneration in the central and peripheral nervous systems. The focus of the research group lies in the underlying signalling mechanisms associated with neurological conditions such as Parkinson's or Alzheimer's disease. The perspective article relates to our recent studies on α-synuclein signalling in synaptic physiology and its associated function and dysfunction in Parkinson's disease. This study was a collaborative approach between Flaviano Giorgini's research group including Carlo Breda to characterise α-synuclein signalling in a *Drosophila* model of Parkinson's disease. Giorgini is a leading scientist in the field of neurodegenerative diseases, utilising the fruit fly and yeast models.

PUBLIC INTEREST STATEMENT

This article provides a discussion of the ongoing research and available data on α-synuclein signalling within the scientific community. The article focuses on the neurological effects of α-synuclein signalling in health and disease, with specific contributions to Parkinson's disease pathology. We have recently published an article presenting data how α-synuclein signalling can be modulated and we are discussing these results here in the context of Parkinson's disease and neuronal/synaptic dysfunction.

neurons and the development of Lewy bodies and Lewy neurites. The main component of these inclusions is α-synuclein (Spillantini et al., 1997) which plays a crucial role in the pathogenesis of PD (Singleton et al., 2003). However, the aetiopathology of cell death remains largely unknown, although many, varied and often interacting mechanisms have been proposed, including mitochondrial dysfunction, inflammation, oxidative stress, genetic/environmental factors and normal ageing (Chan et al., 2007; Gasser, 2010; Schapira, 2008; Sulzer, 2007). These defects are not necessarily limited to DA neurons, but include other classes of neurons in additional brain regions, such as neurons of the locus coeruleus (Gesi et al., 2000) and the pedunculopontine nucleus (Del Tredici & Braak, 2013; Hirsch, Graybiel, Duyckaerts, & Javoy-Agid, 1987).

So why are the dopaminergic neurons so susceptible to insults leading to synaptic loss and neuronal death in PD? The reasons are still unclear, but studies point towards the high energetic demand of these cells as a possible reason for vulnerability. For instance, unlike other neuron types, DA neurons feature a massive, and importantly unmyelinated, innervation of the forebrain (Hernandez et al., 2012) and an extremely high number of synapses with associated high DA release and uptake mechanisms (Andén, Fuxe, Hamberoer, & Hökfelt, 1966; Matsuda et al., 2009). Indeed, quantitative anatomical data suggest that each DA neuron in the rat gives rise to ~100,000–250,000 synapses in the striatum (Bolam & Pissadaki, 2012), which is ~10–1,000-fold higher than striatal spiny neurons (~300 synapses), striatal inhibitory interneurons (~5,000 synapses) (Bevan, Booth, Eaton, & Bolam, 1998; Kawaguchi, Wilson, & Emson, 1990; Kita & Kita, 1994; Tepper & Bolam, 2004) and cortical neurons (~10,000 synapses) (Lacey et al., 2005).

Dopaminergic synapses release neurotransmitters at extremely high levels (Bolam & Pissadaki, 2012); during each release, synaptic soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-complex assembly and disassembly generates highly reactive unfolded SNARE protein intermediates (Hernandez et al., 2012; Lang, Margittai, Holzler, & Jahn, 2002). Thus, these terminals are potentially vulnerable to activity-dependent degeneration, with much evidence pointing to these presynaptic mechanisms as an initiation site for neurodegeneration (Gray et al., 2009). α-synuclein binds directly to SNARE protein synaptobrevin-2/vesicle-associated membrane protein 2 (VAMP2), acting as a chaperone for SNARE complexes (Chandra, Gallardo, Fernández-Chacón, Schlüter, & Südhof, 2005), thereby promoting SNARE-complex assembly (Burre et al., 2010). Interestingly, Rab GTPases can interact with components of the SNARE complex (e.g. syntaxin 4) and have been implicated in regulating vesicle trafficking from the Golgi apparatus and exocytic events of vesicle fusion (Band et al., 2002; Grigoriev et al., 2011; Takahashi et al., 2012). Data also suggest that at least three Rab proteins—Rab11, 17 and 25—are involved in regulating apical targeting of transported vesicles (Prekeris, Klumperman, & Scheller, 2000). A potential link between PD and Rab function is supported by the finding that Rab11 is involved in regulating dopamine transporter trafficking (Furman, Lo, Stokes, Esteban, & Gnegy, 2009). Thus, dysfunctional α-synuclein may contribute to synaptic loss in degeneration, in particular in dopaminergic neurons, which could be linked to Rab functions associated with vesicle trafficking and release mechanisms.

Neuronal activity depends on healthy synaptic function which in turn relies on a multitude of signalling pathways involved in vesicle release and recycling. A lack of α-synuclein function, as seen in PD, has been shown in DA neurons to cause an alteration of expression and subcellular distribution of synapsin III (Zaltieri et al., 2015), a molecule involved in vesicle release. This has been further associated with a rearrangement of synaptic vesicle clusters (Zaltieri et al., 2015), suggesting that α-synuclein is able to affect vesicle pool availabilities or function (Figure 1). In addition, data suggest that the absence of α-synuclein promotes the transport of vesicles from the reserve pool to the readily releasable pools within the synapse (Abeliovich et al., 2000) and that α-synuclein can possibly interfere with a late step in exocytosis (Larsen et al., 2006). As α-synuclein affects DA release by modulating release probabilities (Senior et al., 2008), it is conceivable that this is one route by which α-synuclein dysfunction is linked to dopaminergic neuronal failure. Thus, it appears that α-synuclein may be a negative regulator of neurotransmitter release, by modulating both the rate of transfer of vesicles to the readily releasable pool and the probability of vesicle fusion following synaptic

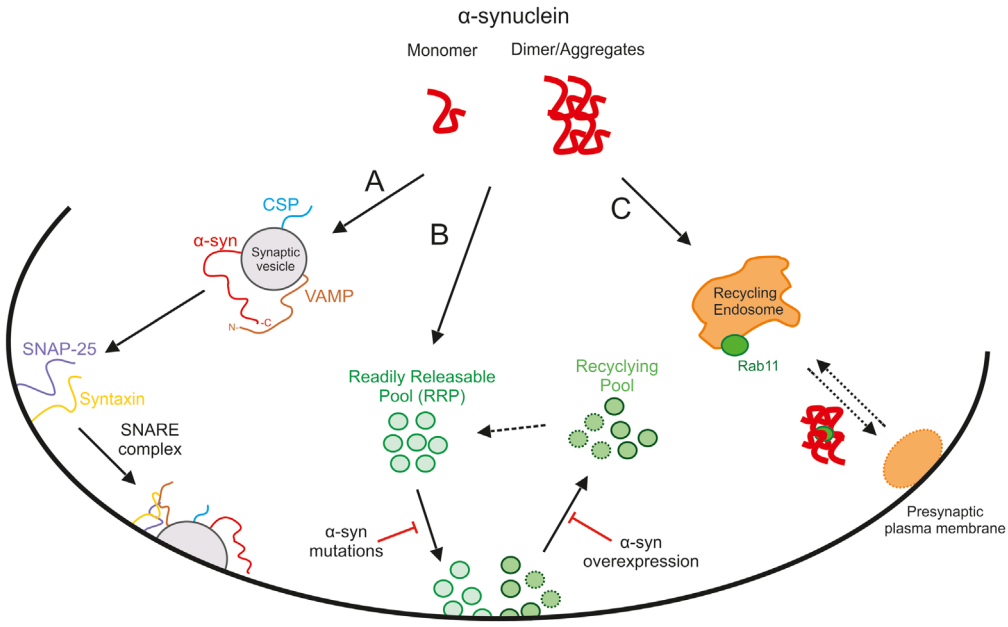

Figure 1. Schematic model of α-synuclein involvement at synapses.

Notes: (A) At the level of synaptic vesicles, the C-terminal of α-synuclein binds to the N-terminal of VAMP, facilitating the formation of the SNARE complex. Once the vesicle binds to syntaxin and SNAP-25, the SNARE complex is assembled and the neurotransmitter is released. (B) Release of dopamine neurotransmitter is decreased when α-synuclein is overexpressed or mutated. High levels of α-synuclein reduce the availability of synaptic vesicles in the recycling pool by affecting vesicle endocytosis. Mutations in α-synuclein (E46K or A53T) reduce neurotransmitter release by impairing late stages of exocytosis. (C) By interacting with Rab11, α-synuclein perturbs vesicle trafficking and, in particular, the recycling endosomal pathway—contributing to the accumulation of misfolded and aggregated α-synuclein in neurons.

stimulation. This specific mode of action could relate to the endogenous function of α-synuclein, as evidence implies that the physiological role of α-synuclein is to contribute to exocytosis of neurotransmitters at the synapse.

Associated with the enormous number of dopaminergic synapses, the axonal length of these neurons exceeds that of most other neuron types (Bolam & Pissadaki, 2012). As a result, dysfunctional protein trafficking within these exceptionally long axons could pose an additional risk for DA neurons (Hunn, Cragg, Bolam, Spillantini, & Wade-Martins, 2015). Indeed, trafficking of vesicles (e.g. synaptic neurotransmitter vesicles), mitochondria and ribosomes throughout the cell is dependent upon transport along microtubules, which when impaired could particularly compromise these neurons.

In this context, our recent publication in *Human Molecular Genetics* has reported that restoration of vesicular trafficking ameliorates phenotypes induced by α-synuclein overexpression (Breda et al., 2015). Using a *Drosophila* model of PD, we tested whether α-synuclein expression affects larval NMJ function and adult fly phenotypes. Here, we found that Rab11, a small GTPase involved in trafficking of vesicles between the recycling endosome/plasma membrane (Hales, Vaerman, & Goldenring, 2002) and the *trans*-Golgi network (Stenmark, 2009; Wilcke et al., 2000), reverses synaptic effects caused by α-synuclein, rescues degeneration of dopaminergic neurons, reduces protein aggregation and ameliorates behavioural defects.

Our work suggests that Rab signalling can modulate α-synuclein-mediated synaptic dysfunction (Breda et al., 2015). Given the ubiquitous expression of Rab11, its localisation to synaptic boutons (Chan et al., 2011) and the interaction of α-synuclein with Rab GTPases (Gitler et al., 2008), it is likely that Rab11 performs a general role in maintaining synaptic function, possibly via Rab-interacting molecules (RIMs), known mediators of synaptic homeostasis (Müller, Liu, Sigrist, & Davis, 2012; Müller, Pym, Tong, & Davis, 2011). This broad action of Rab11 has also been seen in a *Drosophila* model of Huntington's disease (Steinert et al., 2012; Giorgini & Steinert, 2013), further supporting the notion of essential RIM-mediated signalling in this disorder. Thus, Rab11 may be involved in rescuing α-synuclein-induced defects, and further implicates this part of synapse function and maintenance in therapeutic strategies (Agola, Jim, Ward, BasuRay, & Wandinger-Ness, 2011).

In total, although PD is characterised by a myriad of different symptoms, α-synuclein signalling at the synapse may be crucially involved in the pathogenesis of the disease, possibly at early stages of its progression. This dysfunction—at least in part—could be due to compromised trafficking, metabolic alterations and the resulting modulation of synaptic release signalling pathways (i.e. SNARE complex and RIM function). Thus, the connection between activity at synapses and dopaminergic transmission with protein trafficking may ultimately help to pinpoint new therapeutic targets in neuronal dysfunction.

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Competing interests
The authors declare no competing interest.

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References

Abeliovich, A., Schmitz, Y., Fariñas, I., Choi-Lundberg, D., Ho, W. H., Castillo, P. E., … Rosenthal, A. (2000). Mice lacking α-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron, 25*, 239–252. http://dx.doi.org/10.1016/S0896-6273(00)80886-7

Agola, J. O., Jim, P. A., Ward, H. H., BasuRay, S., & Wandinger-Ness, A. (2011). Rab GTPases as regulators of endocytosis, targets of disease and therapeutic opportunities. *Clinical Genetics, 80*, 305–318. http://dx.doi.org/10.1111/cge.2011.80.issue-4

Andén, N. E., Fuxe, K., Hamberoer, B., & Hökfelt, T. (1966). A quantitative study on the nigro-neostriatal dopamine neuron system in the rat. *Acta Physiologica Scandinavica, 67*, 306–312. http://dx.doi.org/10.1111/apha.1966.67.issue-3-4

Band, A. M., Ali, H., Vartiainen, M. K., Welti, S., Lappalainen, P., Olkkonen, V. M., & Kuismanen, E. (2002). Endogenous plasma membrane t-SNARE syntaxin 4 is present in Rab11 positive endosomal membranes and associates with cortical actin cytoskeleton. *FEBS Letters, 531*, 513–519. http://dx.doi.org/10.1016/S0014-5793(02)03605-0

Bevan, M. D., Booth, P. A., Eaton, S. A., & Bolam, J. P. (1998). Selective innervation of neostriatal interneurons by a subclass of neuron in the globus pallidus of the rat. *The Journal of Neuroscience,* 18, 9438–9452.

Bolam, J. P., & Pissadaki, E. K. (2012). Living on the edge with too many mouths to feed: Why dopamine neurons die. *Movement Disorders, 27*, 1478–1483. http://dx.doi.org/10.1002/mds.v27.12

Breda, C., Nugent, M. L., Estranero, J. G., Kyriacou, C. P., Outeiro, T. F., Steinert, J. R., & Giorgini, F. (2015). Rab11 modulates alpha-synuclein-mediated defects in synaptic transmission and behaviour. *Human Molecular Genetics, 24*, 1077–1091. http://dx.doi.org/10.1093/hmg/ddu521

Burre, J., Sharma, M., Tsetsenis, T., Buchman, V., Etherton, M. R., & Sudhof, T. C. (2010). Alpha-synuclein promotes SNARE-complex assembly *in vivo* and *in vitro*. *Science, 329*, 1663–1667. http://dx.doi.org/10.1126/science.1195227

Chan, C. C., Scoggin, S., Wang, D., Cherry, S., Dembo, T., Greenberg, B., … Hiesinger, P. R. (2011). Systematic discovery of Rab GTPases with synaptic functions in Drosophila. *Current Biology, 21*, 1704–1715. http://dx.doi.org/10.1016/j.cub.2011.08.058

Chan, C. S., Guzman, J. N., Ilijic, E., Mercer, J. N., Rick, C., Tkatch, T., … Surmeier, D. J. (2007). "Rejuvenation" protects neurons in mouse models of Parkinson's disease. *Nature, 447*, 1081–1086. http://dx.doi.org/10.1038/nature05865

Chandra, S., Gallardo, G., Fernández-Chacón, R., Schlüter, O. M., & Südhof, T. C. (2005). α-Synuclein cooperates with CSPα in preventing neurodegeneration. *Cell, 123*, 383–396. http://dx.doi.org/10.1016/j.cell.2005.09.028

de Lau, L. M., & Breteler, M. M. (2006). Epidemiology of Parkinson's disease. *The Lancet Neurology, 5*, 525–535. http://dx.doi.org/10.1016/S1474-4422(06)70471-9

de Rijk, M. C., Breteler, M. M., Graveland, G. A., Ott, A., Grobbee, D. E., van der Meche, F. G., & Hofman, A. (1995). Prevalence of Parkinson's disease in the elderly: The Rotterdam study. *Neurology, 45*, 2143–2146. http://dx.doi.org/10.1212/WNL.45.12.2143

Del Tredici, K., & Braak, H. (2013). Dysfunction of the locus coeruleus-norepinephrine system and related circuitry in Parkinson's disease-related dementia. *Journal of Neurology, Neurosurgery & Psychiatry, 84*, 774–783. http://dx.doi.org/10.1136/jnnp-2011-301817

Furman, C. A., Lo, C. B., Stokes, S., Esteban, J. A., & Gnegy, M. E. (2009). Rab 11 regulates constitutive dopamine transporter trafficking and function in N2A neuroblastoma cells. *Neuroscience Letters, 463*, 78–81. http://dx.doi.org/10.1016/j.neulet.2009.07.049

Gasser, T. (2010). Identifying PD-causing genes and genetic susceptibility factors: Current approaches and future prospects. *Progress in Brain Research, 183*, 3–20.

Gesi, M., Soldani, P., Giorgi, F. S., Santinami, A., Bonaccorsi, I., & Fornai, F. (2000). The role of the locus coeruleus in the development of Parkinson's disease. *Neuroscience & Biobehavioral Reviews, 24*, 655–668. http://dx.doi.org/10.1016/S0149-7634(00)00028-2

Giorgini, F., & Steinert, J. R. (2013). Rab11 as a modulator of synaptic transmission. *Communicative & Integrative Biology, 6*, e26807.

Gitler, A. D., Bevis, B. J., Shorter, J., Strathearn, K. E., Hamamichi, S., Su, L. J., … Lindquist, S. (2008). The Parkinson's disease protein alpha-synuclein disrupts cellular Rab homeostasis. *Proceedings of the National Academy of Sciences, 105*, 145–150. http://dx.doi.org/10.1073/pnas.0710685105

Gray, B. C., Siskova, Z., Perry, V. H., & O'Connor, V. (2009). Selective presynaptic degeneration in the synaptopathy associated with ME7-induced hippocampal pathology. *Neurobiology of Disease, 35*, 63–74. http://dx.doi.org/10.1016/j.nbd.2009.04.001

Grigoriev, I., Yu, K. L., Martinez-Sanchez, E., Serra-Marques, A., Smal, I., Meijering, E., ... Akhmanova, A. (2011). Rab6, Rab8, and MICAL3 cooperate in controlling docking and fusion of exocytotic carriers. *Current Biology, 21*, 967–974. http://dx.doi.org/10.1016/j.cub.2011.04.030

Hales, C. M., Vaerman, J. P., & Goldenring, J. R. (2002). Rab11 family interacting protein 2 associates with myosin Vb and regulates plasma membrane recycling. *Journal of Biological Chemistry, 277*, 50415–50421. http://dx.doi.org/10.1074/jbc.M209270200

Hernandez, J. M., Stein, A., Behrmann, E., Riedel, D., Cypionka, A., Farsi, Z., ... Jahn, R. (2012). Membrane fusion intermediates via directional and full assembly of the SNARE complex. *Science, 336*, 1581–1584. http://dx.doi.org/10.1126/science.1221976

Hirsch, E. C., Graybiel, A. M., Duyckaerts, C., & Javoy-Agid, F. (1987). Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. *Proceedings of the National Academy of Sciences, 84*, 5976–5980. http://dx.doi.org/10.1073/pnas.84.16.5976

Hunn, B. H., Cragg, S. J., Bolam, J. P., Spillantini, M. G., & Wade-Martins, R. (2015). Impaired intracellular trafficking defines early Parkinson's disease. *Trends in Neurosciences, 38*, 178–188. http://dx.doi.org/10.1016/j.tins.2014.12.009

Kawaguchi, Y., Wilson, C. J., & Emson, P. C. (1990). Projection subtypes of rat neostriatal matrix cells revealed by intracellular injection of biocytin. *The Journal of Neuroscience, 10*, 3421–3438.

Kita, H., & Kita, S. T. (1994). The morphology of globus pallidus projection neurons in the rat: An intracellular staining study. *Brain Research, 636*, 308–319. http://dx.doi.org/10.1016/0006-8993(94)91030-8

Lacey, C. J., Boyes, J., Gerlach, O., Chen, L., Magill, P. J., & Bolam, J. P. (2005). GABA(B) receptors at glutamatergic synapses in the rat striatum. *Neuroscience, 136*, 1083–1095. http://dx.doi.org/10.1016/j.neuroscience.2005.07.013

Lang, T., Margittai, M., Holzler, H., & Jahn, R. (2002). SNAREs in native plasma membranes are active and readily form core complexes with endogenous and exogenous SNAREs. *The Journal of Cell Biology, 158*, 751–760. http://dx.doi.org/10.1083/jcb.200203088

Larsen, K. E., Schmitz, Y., Troyer, M. D., Mosharov, E., Dietrich, P., Quazi, A. Z., ... Sulzer, D. (2006). Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. *Journal of Neuroscience, 26*, 11915–11922. http://dx.doi.org/10.1523/JNEUROSCI.3821-06.2006

Matsuda, W., Furuta, T., Nakamura, K. C., Hioki, H., Fujiyama, F., Arai, R., & Kaneko, T. (2009). Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. *Journal of Neuroscience, 29*, 444–453. http://dx.doi.org/10.1523/JNEUROSCI.4029-08.2009

Müller, M., Liu, K. S., Sigrist, S. J., & Davis, G. W. (2012). RIM controls homeostatic plasticity through modulation of the readily-releasable vesicle pool. *Journal of Neuroscience, 32*, 16574–16585. http://dx.doi.org/10.1523/JNEUROSCI.0981-12.2012

Müller, M., Pym, E. C., Tong, A., & Davis, G. W. (2011). Rab3-GAP controls the progression of synaptic homeostasis at a late stage of vesicle release. *Neuron, 69*, 749–762. http://dx.doi.org/10.1016/j.neuron.2011.01.025

Prekeris, R., Klumperman, J., & Scheller, R. H. (2000). A Rab11/Rip11 protein complex regulates apical membrane trafficking via recycling endosomes. *Molecular Cell, 6*, 1437–1448. http://dx.doi.org/10.1016/S1097-2765(00)00140-4

Schapira, A. H. (2008). Mitochondria in the aetiology and pathogenesis of Parkinson's disease. *The Lancet Neurology, 7*, 97–109. http://dx.doi.org/10.1016/S1474-4422(07)70327-7

Senior, S. L., Ninkina, N., Deacon, R., Bannerman, D., Buchman, V. L., Cragg, S. J., & Wade-Martins, R. (2008). Increased striatal dopamine release and hyperdopaminergic-like behaviour in mice lacking both alpha-synuclein and gamma-synuclein. *European Journal of Neuroscience, 27*, 947–957. http://dx.doi.org/10.1111/j.1460-9568.2008.06055.x

Singleton, A. B., Farrer, M., Johnson, J., Singleton, A., Hague, S., Kachergus, J., ... Gwinn-Hardy, K. (2003). Alpha-synuclein locus triplication causes Parkinson's disease. *Science, 302*, 841. http://dx.doi.org/10.1126/science.1090278

Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). Alpha-synuclein in Lewy bodies. *Nature, 388*, 839–840. http://dx.doi.org/10.1038/42166

Steinert, J. R., Campesan, S., Richards, P., Kyriacou, C. P., Forsythe, I. D., & Giorgini, F. (2012). Rab11 rescues synaptic dysfunction and behavioural deficits in a Drosophila model of Huntington's disease. *Human Molecular Genetics, 21*, 2912–2922. http://dx.doi.org/10.1093/hmg/dds117

Stenmark, H. (2009). Rab GTPases as coordinators of vesicle traffic. *Nature Reviews Molecular Cell Biology, 10*, 513–525. http://dx.doi.org/10.1038/nrm2728

Sulzer, D. (2007). Multiple hit hypotheses for dopamine neuron loss in Parkinson's disease. *Trends in Neurosciences, 30*, 244–250. http://dx.doi.org/10.1016/j.tins.2007.03.009

Takahashi, S., Kubo, K., Waguri, S., Yabashi, A., Shin, H. W., Katoh, Y., & Nakayama, K. (2012). Rab11 regulates exocytosis of recycling vesicles at the plasma membrane. *Journal of Cell Science, 125*, 4049–4057. http://dx.doi.org/10.1242/jcs.102913

Tepper, J. M., & Bolam, J. P. (2004). Functional diversity and specificity of neostriatal interneurons. *Current Opinion in Neurobiology, 14*, 685–692. http://dx.doi.org/10.1016/j.conb.2004.10.003

Wilcke, M., Johannes, L., Galli, T., Mayau, V., Goud, B., & Salamero, J. (2000). Rab11 regulates the compartmentalization of early endosomes required for efficient transport from early endosomes to the trans-Golgi network. *The Journal of Cell Biology, 151*, 1207–1220. http://dx.doi.org/10.1083/jcb.151.6.1207

Zaltieri, M., Grigoletto, J., Longhena, F., Navarria, L., Favero, G., Castrezzati, S., ... Bellucci, A. (2015). Alpha-synuclein and synapsin III cooperatively regulate synaptic function in dopamine neurons. *Journal of Cell Science, 128*, 2231–2243. http://dx.doi.org/10.1242/jcs.157867

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