Endocytosis is an essential cellular process required for multiple physiological functions, including communication with the extracellular environment, nutrient uptake, and signaling by the cell surface receptors. In a broad sense, endocytosis is accomplished through either constitutive or ligand-induced invagination of the plasma membrane, which results in the formation of the plasma membrane-retrieved endocytic vesicles, which can either be sent for degradation to the lysosomes or recycled back to the PM. This additional function of endocytosis in membrane retrieval has been adopted by excitable cells, such as neurons, for membrane equilibrium maintenance at synapses. The last two decades were especially productive with respect to the identification of brain-specific functions of the endocytic machinery, which additionally include but not limited to regulation of neuronal differentiation and migration, maintenance of neuron morphology and synaptic plasticity, and prevention of neurotoxic aggregates spreading. In this review, we highlight the current knowledge of brain-specific functions of endocytic machinery with a specific focus on three brain cell types, neuronal progenitor cells, neurons, and glial cells.
Introduction

Cells are isolated from their surrounding environment by the plasma membrane (PM), a structure composed of a lipid bilayer and proteins. To communicate with the extracellular environment and absorb nutrients that cannot pass through the PM, cells rely on a process called endocytosis (from Greek: endon – within; kytos – cell; and ois – process). In a broad sense, endocytosis is defined as the invagination (or the protrusion) of the PM, which can be coupled with the engulfing and internalization of bioactive molecules or genetic materials. The result of this process is an intracellular membrane vesicle, which is formed by the scission of the PM. Endocytic vesicles are key players of routine cellular life. Endocytosis is essential for several critical cellular processes, such as nutrient uptake, PM remodeling, and intracellular signaling [1,2].

Cells have evolved several distinct pathways to perform endocytosis. They include two simple modes, macropinocytosis and phagocytosis, in which PM protrusions mediate the bulk uptake of extracellular particles or large liquid volume in a highly energy-demanding fashion [3]. For the selective uptake of molecules, cells use receptor-mediated endocytosis, which allows an increase in the concentration of macromolecules at the PM by means of membrane-localized receptors and reduces the energy consumption necessary for their internalization. The formation of membrane vesicles during receptor-mediated endocytosis requires several key components, including scaffold protein clathrin and its accessory adaptor proteins [4,5]. In fact, when vesicles form by receptor-mediated endocytosis, they possess a characteristic lattice-like clathrin coat, a phenomenon, which defines this process as clathrin-mediated endocytosis (CME) [6]. Selective uptake of extracellular ligands and receptors from the PM can also occur by a mechanism that does not require clathrin. For this process, several cell types, including neurons, use clathrin-independent endocytosis (CIE), where the ruffling of the PM allows for membrane retrieval, coupled with endocytic uptake of ligands (growth factors or cytokines), bacterial toxins, and/or viruses [3,7].

It is likely that endocytosis has evolved in all known eukaryotic cells for two major reasons: (a) to bring nutrients into cells and (b) to sample the cell’s environment for growth and guidance cues. Both result in either constitutive or ligand-induced (e.g., epidermal growth factor, EGF) formation of PM-retrieved endocytic vesicles, which can either be sent for degradation to lysosomes or recycled back to the PM. This additional function of endocytosis in PM retrieval has been adopted by excitable cells, such as neurons, to maintain membrane equilibrium maintenance at synapses. Unlike constitutive or ligand-induced membrane retrieval in nonexcitable cells, CME and CIE in neurons can be additionally activated by electrical activity and used to recycle synaptic vesicles (SV) materials and maintain the SV pool. Apart from cycles of exo/endocytosis of SVs, brain-specific functions of endocytosis include the propagation of neurotrophin signaling from the distal axons toward the cell body [8–10], regulation of neural development by the orchestrated action of guidance receptors and adhesion molecules [11,12], and the maintenance of synaptic plasticity [13].

In this review, we first briefly outline basic mechanisms of endocytosis and then summarize the current state of knowledge with respect to the functions of endocytic machinery in the brain, focusing on three main types of brain cells: neuronal progenitor cells, neurons, and glial cells. We note that this review highlights endocytic pathways occurring at the PM (and/or noncanonical functions of ‘classical’ endocytosis proteins) and is not focused on the role of endosomes and/or endosome trafficking in the brain.

Basic mechanisms of endocytosis

Macropinocytosis

Macropinocytosis is a highly conserved actin-driven endocytic process for the nonspecific bulk internalization of extracellular fluid, membrane, and other particles into large vacuoles (> 0.2–8 µm) [14]. It is initiated by a variety of external stimuli (including growth factors, bacteria, and viruses) and is executed as membrane ruffling that can fold back on the PM, forming a macropinocytic cup. Subsequent closure of the macropinocytic cup forms a large vacuole, called the macropinosome [15]. Fission of the macropinosome from the PM and delivery of extracellular fluid to lysosomes is the culminating point of macropinocytosis. Macropinocytosis is a receptor (and cargo)-independent process, but how precisely the formation of macropinocytic cup is achieved is only emerging in understanding [16]. Key players of macropinocytosis include several small GTPases, cytoskeletal proteins (e.g., WASP, ARP2/3), and inositol phospholipids [17]. With respect to the role in macropinocytosis, the most characterized of these components are the RAS superfamily of GTPases (e.g., RAC1, CDC42, RAS, ARF6), which are known as master regulators of the actin cytoskeleton rearrangement [18–20], and three kinases, the phosphoinositol (PI) 3-kinase (PI3K), the PI 4-phosphate 5-kinase (PI(4)P5K), and the
phospholipase C-γ-kinase (PLCγ) [21]. PI3K and PI4P5K orchestrate the sequential transition of PIs (mainly PI(4,5)P2 and PI(3,4,5)P3) in membrane ruffles, which can then recruit and stimulate the activity of several actin-regulatory proteins, including RAC1 [22]. Hydrolysis of PI(4,5)P2 by PLCγ generates diacyl-glycerol (DAG) (together with inositol-1,4,5-trisphosphate (I(1,4,5)P3)), which remains associated with the membrane of the macropinocytic cup, where it then recruits and activates protein kinase Cα (PKCα) and PKCε. After association with the PM, PKC promotes ruffles and the formation of macropinosomes [23]. The activation of PLCγ and PI3K during macropinocytosis can be achieved via growth factor-bound receptors [24,25]. Cells can maintain high macropinocytosis rates for hours [26], and this ability is utilized extensively by cancer and immune cells using this pathway to obtain nutrients from the extracellular space [27] and to capture antigens for presentation to T cells [28], respectively. In comparison with non-neuronal cells, the function of this pathway in the brain is just emerging in understanding and is discussed below.

**Clathrin-mediated endocytosis**

Clathrin-mediated endocytosis involves the assembly of a coated pit on the PM, which induces the formation of a morphologically well-defined coated vesicle approximately 50 nm in size, and requires the involvement of clathrin, a triskelion-shaped scaffold protein [29–31]. Clathrin molecules polymerize around the cytoplasmic face of the coated pit and act as a reinforced cage for the formation of CME vesicle [2]. CME is initiated by the recruitment of cargo adaptors, such as FCHO [32], EPS15 [33], stonins [34], the assembly protein (AP) complex 2 (AP-2) [35], as well as membrane bending-inducing proteins (e.g., epsin, AP180, or CALM) to the PM [36–40]. These serve to link clathrin to the PM via their association with PIs, in particular with the PM-enriched PI(4,5)P2 [41]. AP-2 is the major clathrin adaptor protein for the CME [42,43]. It harbors several PI(4,5)P2-binding sites [44,45] and interacts with a cargo containing either tyrosine- or dileucine-based motifs [46–48]. AP-2 recruitment to the PM can be activated by phosphorylation of the µ2 subunit by the kinase AAK1 [49,50]. Due to the ability of AP-2 to simultaneously associate with the PM and the transmembrane cargo, it coordinates the concentration of proteins destined for the internalization in the coated pit [51]. A mature clathrin-coated vesicle is generated by the fission of an assembled coated pit from the PM [52], a process which requires the action of GTPase dynamin, and the involvement of bni/ampiphysin/RVS167 (BAR) domain protein family members (e.g., endophilin A1-3) and the actin cytoskeleton [2,53–60]. In conjunction with or shortly after the fission, released CME vesicles shed their coat by the coordinated action of the PI(4,5)P2-phosphatase synaptojanin-1 (SYNJ1) [61,62] and the clathrin disassembling chaperone heat-shock cognate 70 along with its cofactor auxilin [63,64]. The CME vesicle is subsequently targeted to the RAB5-positive early endosome, from where the cargo can either be recycled back to the PM (via the RAB11-positive recycling endosome) or sent to the lysosome for the degradation. CME constitutes the main entry route for majority of surface receptors and their ligands in various cell types [65] and is essential for nutrient acquisition, the composition of the PM, cell surface receptor signaling [66,67], as well as regulation of cellular ion homeostasis [68]. In the brain, CME additionally internalizes transmembrane receptors together with their extracellular ligands [9] and recycles SVs material during presynaptic endocytosis [69]. CME is also crucial for neurogenesis and neurodevelopment, as discussed in detail below.

**Clathrin-independent endocytosis**

The term CIE was initially used to describe the macro (or micro)–pinocytosis pathways, depending on the size of formed vesicles [70]. Today, CIE is defined as a form of endocytic uptake by membrane structures in the range of 50–200 nm, devoid of a clathrin coat. CIE pathways can be classified based on the key molecular component (e.g., fast endophilin-mediated endocytosis [71]), the speed of the process (ultrafast endocytosis [72]), or the PM marker (caveolin- or flotillin-associated endocytosis) [73–76]. It is worth mentioning that the involvement of flotillin micro-domains in endocytosis has been questioned in the recent literature [7]. CIE is not present constitutively in cells and can be activated by ligands (growth factors or cytokines), bacterial toxins, and/or viruses [76]. The precise molecular mechanisms of CIE are just emerging in understanding, and the core molecular machinery identified thus far involves actin-polymerization factors, BAR domain proteins, and dynamin [77–80]. Material carried by CIE vesicles includes EGF-, interleukin-2-, and insulin-bound receptors, and cholera toxin, among others [81]. Interestingly, Caveolins (the resulting bulb-shaped surface pits of caveolin-associated endocytosis), contrary to clathrin-coated pits, are described as very sparse in neuronal cells [82–85]. Nevertheless, neurons express Caveolin 1 (Cav1)
and/or Cav1-interacting proteins [86], suggesting a noncanonical function of Cav1 in neuronal signaling. Flotillin-associated endocytosis regulates neurodevelopment, synaptogenesis, and receptor tyrosine kinase (RTK) signaling in the brain. However, it is currently unclear if the regulation of these functions is due to the direct role of flotillin in CIE [76]. Contrary to this, the role of ultrafast endocytosis is well described in the brain, where its ability to act faster than the CME was exploited by synapses to perform compensatory PM retrieval following exocytosis of SVs [87].

Role of endocytosis in neuronal progenitor cells

Neural progenitor cells (NPCs) are the multipotent stem cells of the central nervous system (CNS) that give rise to all neuronal cell types populating the brain [88]. NPCs located within the ‘ventricular zone (VZ)’, which is the primary proliferative zone during brain development [89], are known as ‘radial glia’ (RG) cells [90]. During embryonic development, RG cells undergo extensive mitosis, whereby symmetric divisions generate two daughter cells that retain NPC properties. At the onset of cortical neurogenesis, RG cells start to undergo mitosis through asymmetric divisions, which produces a self-renewed RG cell and a neuronal daughter cell (or one RG cell and one basal progenitor, also called intermediate progenitor) [91,92]. Research during the last two decades provides strong evidence for endocytosis having a pivotal role in regulating RG cell asymmetric cell division, where it controls the asymmetrical partitioning of the PM-localized receptors and ligands (cell determinants) into two daughter cells, thus allowing a temporal and spatial regulation of neuronal differentiation (Fig. 1) [11]. This process, among others, is orchestrated by the endocytic protein NUMB [93]. NUMB is a PM-associated cell fate determinant, initially discovered in Drosophila, where when mutated it removes most of the peripheral sensory neurons [94]. Subsequently, it was discovered that NUMB via its direct association with the α-subunit of the AP-2 complex and endocytic protein EPS15, functions as an endocytosis adaptor [12,93,95]. NUMB endocytic activity can also be regulated by the kinase AAK1, which, when overexpressed, induces NUMB redistribution to perinuclear endosomes [96]. During the mitosis of RG cells, interaction with the Golgi component ACBD3 [97] allows for asymmetrical localization of NUMB to the apical membrane, leading to its subsequent segregation to only one daughter cell that remains a progenitor [98]. Its function in endocytosis during development includes the internalization of Notch [99], integrin [100], and RTK [101] receptors. For instance, NUMB mediates the internalization of Notch, which reduces Notch receptor levels at the PM, thereby diminishing Notch signaling. Reduced Notch signaling then promotes neural differentiation [102]. Of note, Notch signaling in non-neuronal cells can also be regulated by AAK1 [103]. Additionally, NUMB influences cell fate by mediating the asymmetric localization of the α subunit of the AP-2 complex [99]. NUMB knockout (KO) mice display premature neuronal differentiation in the brain, though this function might be brain region-specific [98,104]. Interestingly, NUMB-containing daughter cell will remain a progenitor at mouse embryonic day 10 (E10), while the cell inheriting NUMB during the corticogenesis at E13 will become a neuron [11,105,106], implying that NUMB functions to regulate the balance between symmetric proliferative, asymmetric neurogenic, and symmetric neurogenic NPC divisions.

Neural progenitor cells proliferation might also be regulated via formin-dependent CIE endocytosis [107]. In this pathway, the actin-nucleating protein formin 2 together with another actin-binding protein FlnA mediates the endocytosis of the Frizzled co-receptor LRP6, thereby regulating the GSK3β- and β-catenin-independent signaling to direct neuronal proliferation [108]. This pathway, known as canonical WNT signaling pathway, is crucial not only for establishing the telencephalon during development [109] but also for adult neurogenesis [110]. WNT signaling pathway is also regulated by the CME [111]. Clathrin and AP-2 have been proposed to regulate the assembly of LRP6 signalosomes, while the kinase AAK1 has been recently described to promote the clearance of LRP6 from the PM [112]. Whether this function of CME machinery is crucial for the WNT signaling in NPCs has not yet been tested.

Does endocytosis directly regulate the mitosis of NPCs? Although the activity of endocytic processes during mitosis is suggested to be inhibited during mitosis [113–116], an increasing number of endocytic proteins are described to be present at the centrosome, the mitotic spindle, or the mid-body. These include clathrin and epsin proteins, which localize to mitotic spindles and regulate the stability of kinetochore fibers and spindle morphology, independent of their canonical functions in CME [117–121]. The β-subunit of the AP-2 complex has been reported to interact with the mitotic checkpoint kinase BubR1 [122], while a CME adaptor protein the autosomal recessive hypercholesterolemia (ARH) [123,124] sorting the members of the LDL receptor superfamily regulates microtubule
nucleation at the centrosome via its interaction with components of γ-tubulin ring complex [125]. Similarly, dynamin 2, a GTPase known to mediate the fission of clathrin-coated vesicles from the PM, is described to localize at the centrosome where it is required for the completion of cytokinesis [126–128]. The fact that dynamin 2 might be indispensable for embryonic development is supported by the study describing a homozygous mutation in DNM2 in patients with a lethal congenital syndrome [129], as well as by early embryonic lethality of dynamin 2 KO mice [130]. Additionally, cytokinesis can be regulated by formins, as it has been shown for Drosophila diaphanous (dia) protein, where its complete loss causes lethality at the onset of pupation [131]. Clathrin- and caveolae-mediated endocytosis has also been shown to constitute an integral part of cytokinesis in zebrafish embryos [132]. Since the mitotic spindle and its orientation are both implicated in the regulation of symmetric and asymmetric cell division of NPCs [133], it is possible, if not likely, that the depletion of CME components will directly affect brain development by compromising NPC function. This hypothesis has not been directly tested, although recently, a 50% decrease in survival rate during the first postnatal week has been described for the mice lacking the clathrin light chain (CLC) a, but not the CLCb isoform [134,135]. In fact, decreased survival, embryonic and/or early postnatal lethality is a hallmark of most mouse models lacking the ‘classical’ CME components, including AP-2, endophilins, CALM, EPS15L1, Epsin, and dynamin 1 [59,136–142]. On the other hand, the defects in the differentiation of the sensory neurons have been described in patients carrying a loss-of-function mutation in the CLTCL1 gene, encoding clathrin heavy-chain isoform 22 [143,144]. Interestingly, this phenotype is independent of the mentioned above role of clathrin in the mitotic spindle organization and is a result of defective early precursor differentiation due to increased secretion of neuropeptide cargo.

Fig. 1. Schematic representation of the key endocytosis pathways and their functions in NPCs. Ligands are represented together with their receptors with a similar color code. Endocytosis is crucial for the generation of new neurons during development, and later in adulthood, CME ensures the distribution of cell determinants, hence balancing the production of neurons or NPCs. In contrast, CIE and macropinocytosis promote the differentiation into neurons.
Besides the CME, the components of macropinocytosis machinery are also crucial for the NPC proliferation and differentiation. RAC1-dependent signaling is required to promote the learning-induced increase in proliferation of neuronal precursors in the adult hippocampus [145], while the proliferation and the differentiation of subventricular zone (SVZ)-resident adult neural stem cells require CDC42 activation [146,147]. Several neurodevelopmental disorders, such as Costello or Noonan syndrome, are due to hyperactivation of RAS-mediated signaling pathway [148,149]. However, it is currently unknown whether this function of the RAS GTPase family in neurodevelopment involves their role in macropinocytosis. Finally, phospholipid kinases are equally crucial for neuronal development [150,151]. For example, PI3K and its downstream effectors (mTOR and AKT), when activated, promote neuronal differentiation [152] and, when downregulated, cause critical differentiation delays [153,154].

Endocytosis is also important to maintain the function of the primary cilium, a hair-like protrusion found in neuroepithelial cells and RG cells. By regulating multiple signaling pathways, such as RTK, hedgehog, WNT, Notch, TGF-β, and mTOR, the primary cilium detects physical and chemical cues from the environment, which is crucial for the establishment of polarity and neuronal differentiation during development [155–157]. The coordination of signaling pathways is achieved by the ciliary membrane, which in contrast to the rest of the PM lacks PI(4,5)P2 [158]. Low levels of PI(4,5)P2 in proximal regions of cilia are maintained among others by OCRL [159], which is an inositol polyphosphate 5-phosphatase acting on PI(4,5)P2 and crucial for clathrin-coated pits dynamics and uncoating [160]. Clathrin-coated vesicles are abundant at the ciliary pocket flanking the primary cilium. In fact, this region serves as a hotspot for exo- and endocytosis, and both processes are indispensable for the regulation of ciliary membrane delivery and retrieval, as well as for mediating the signaling via membrane-localized receptors [161]. In Caenorhabditis elegans, defects in CME-dependent endocytosis result in the expansion of ciliary (and/or preciliary) membrane [162], while endocytosis gain of function has been described to contribute to cilia shortening [163]. The internalization of key ciliary sonic hedgehog pathway receptors LRP2 (megalin), GPR161 and PTCH1, and TGF-β receptors has been reported to require clathrin. Besides clathrin-coated vesicles, caveolae have also been reported to be present at the ciliary pocket [164], while the internalization and lyosomal delivery of PTCH1 were described to be associated with Cave1-positive lipid rafts [165]. Despite this, the precise role caveolae and other forms of CIE at the primary cilium remain to be determined [159].

### Endocytosis functions in developing and migrating neurons

After the RG cells have undergone asymmetric cell division, their committed to differentiate daughter cells migrate to the SVZ, where they divide symmetrically to produce a pair of neurons [92,166–168], further migrating to the cortical plate [88]. Such directional migration requires polarized membrane remodeling and concerted cycles of adhesions and deathadhesion events [169,170]. Endocytosis is indispensable for both of these processes (Fig. 2). For instance, it is involved in the internalization of surface guidance receptors (e.g., N-cadherin, β1-integrin) in migrating NPCs and neurons [171,172] and thus can physically disrupt contacts between cells, and/or between a cell and an extracellular matrix substrate. The fact that endocytosis, and especially CME, is crucial for the adhesion disassembly during cell migration in the brain is supported by the data showing that clathrin-coated pits are enriched at adhesive contacts with matrix substrates in migratory neurons, while inhibition of dynamin and clathrin impairs neuronal migration because of impaired sorting of adhesion proteins [173].

Endocytic adaptor NUMB is found in the complex with several adherent junction proteins (E-cadherin, N-cadherin, and β-catenin), and its inactivation in RG cells causes progenitor dispersion and disorganized cortical lamination [174]. Besides, NUMB regulates the brain-derived neurotrophic factor (BDNF)-driven migration of granule cell precursors in the cerebellum [175]. This polarized chemotaxis of cerebellar NPCs requires the endocytosis of BDNF-activated TRKB receptors at leading processes of the cell, a process which is mediated by NUMB [101]. Interestingly, in sympathetic neurons TRKB endocytosis is regulated by Pincher/RAC-dependent macropinocytosis [176], while in postnatal cortical neurons CME adaptor AP-2 mostly regulates postendocytic trafficking of BDNF-activated TRKB receptors independently of its canonical function in TRKB endocytosis (see below) [136].

Endocytic protein disabled-2 (DAB2, also known as DOC-2), which is known to directly associate with clathrin [177,178] and AP-2 [177–179], contributes to polarized neuronal morphology by regulating the neurite outgrowth via the NGF-mediated signaling [180]. DAB1, which is a close homologue of DAB2, also functions in migrating neurons as a key component of the reelin signaling pathway (via the reelin receptors ApoE receptor 2 (ApoER2)) and very-low-density
Fig. 2. Schematic representation of the key endocytic pathways and their functions in developing and migrating neurons, including their axonal growth cones (insert). Ligands are represented together with their receptors with a similar color code. During migration specifically, CME modulates the adhesion and/or deadhesion of the migrating immature neurons, and later, together with CIE and macropinocytosis, will regulate polarization of neurons (axonal growth and ramification of neuronal processes). In the growth cone, endocytosis pathways regulate local PM remodeling in response to attractive and repulsive signals, and the receptor trafficking upon the chemorepulsion.
lipoprotein receptor (VLDLR), which is a master regulator of neuroblast migration [181]. DAB1 is highly neuron-enriched [182,183], and spontaneous mutations of DAB1 in mice result in abnormal brain development [184,185], suggesting a role in the neural development similar to that of Drosophila DAB [186]. A DAB1 KO in mice causes aberrant cortical lamination and cerebellum development [182], a phenotype identical to that of mice lacking reelin and/or its receptors [181]. The mechanism of DAB1 regulation of reelin signaling involves its direct interaction with the reelin-bound ApoER2 and VLDLR, which increases DAB1 phosphorylation. Whether DAB1 functions in reelin signaling by directly influencing ApoER2 and VLDLR endocytosis is still up for debate, since mice lacking the C-terminal region of DAB1 (naturally occurring DAB1 p45 splice isoform), which bears clathrin adapter AP-2- and SH3-binding sites, are born normal with no severe defects in cortical lamination [187]. Interestingly, DAB1 p45 hemizygous mice reveal a distinct splitting in the stratum pyramidale (SP) in the CA1 region of the hippocampus (some pyramidal cells pass through the SP and form a second layer), suggesting a specific role for the endocytic machinery in regulating migration events of specific neuronal types. This hypothesis was recently proven in another study, where a component of CME machinery Intersectin 1 (ITSN1) [188–190] was identified to associate with the VLDLR and DAB1 and was shown to selectively regulate the splitting of the CA1 [191]. Interestingly, the role of I tsN1 in the VLDLR/DAB1 axis of reelin signaling does not involve its classical role in receptor endocytosis but requires its function as a molecular bridge facilitating the VLDLR/DAB1 association and co-clustering.

Endocytosis might also regulate the neuronal migration in the developing nervous system via the interaction of the µ subunit of AP-2 complex with the microtubule-binding protein doublecortin, which is genetically linked to the X-linked lissencephaly syndrome in humans [192–194]. Doublecortin is prominently expressed in newborn migrating neurons, where it is required for the regulation of microtubule dynamics, dynein-mediated nucleus centrosome coupling, and internalization of cell adhesion L1-CAM family member neurofascin [195,196]. The latter function of doublecortin in neurofascin endocytosis requires its interaction with AP-2, as it has been recently demonstrated by the AP-2 binding-deficient doublecortin mutant [197]. Besides, the CME can also regulate the growth cone motility and neurite outgrowth by directly regulating the AP-2-dependent endocytosis of cell adhesion molecules L1-CAM and N-cadherin [198,199]. Neurite outgrowth was also proposed to be regulated by clathrin assembly proteins AP180 and CALM [200], although the absence of neurodevelopmental defects in AP180 KO mice questions its role in the developing brain [201]. In contrary to this, CALM KO mice have been reported to show retarded growth and reveal significant atrophy of the cortex and ventral enlargement, but this phenotype was not analyzed any further [202]. Finally, a well-known role for the CME pathways in internalization and degradation of the EGF receptor [203] is also important for the developmental regulation of neuronal migration [204,205].

In addition to CME, several other endocytic pathways have been recently described to be required in migrating neurons. For instance, membrane remodeling during the migration of neural crest cells in chicken embryos has been shown to require the F-actin-driven macropinocytosis pathway [206]. This pathway generates macropinosomes, which transport F-actin along microtubules for the adjustment of membrane protrusions, that is, lamellipodia, at the leading edge. Other macropinocytosis players in neuronal migration include ARF6 [207], CDC42 [208], and actin-remodeling proteins [209–212]. In growing neurons, macropinocytosis-mediated massive retrieval of the PM is an important mechanism of growth cone collapse and axon growth inhibition [213,214]. The macropinocytosis-like pathway also mediates the endocytosis of CendR-bound transmembrane receptor Neurorpin1 [215], which is known among others to function in axon guidance via interaction with its ligand SEMA3A [216]. In tumor cells, this pathway is induced by nutrient deprivation, but whether similar is used by neurons remains to be determined. Cav1, the component of the caveolin-mediated endocytosis, promotes both immature neurite pruning and leading process elongation through the endocytosis of N-cadherin and L1 cell adhesion molecules [217], while its loss of function in Xenopus and/or iPSCs-derived human neurons results in altered axonal outgrowth [218,219]. Interestingly, a recent report suggests that axonal extensions of embryonic hippocampal neurons in a 3D environment are driven by microtubule polymerization and do not require adhesions and/or actin involvement [220].

Axon development and establishing of neuronal polarity also require endocytosis. Growing axons use extracellular guidance cues to navigate in the developing nervous system [221]. The mechanism regulating the bidirectional steering of axonal growth cones in response to attractive and repulsive signals requires local PM remodeling, which is achieved by exocytosis and endocytosis imbalance. This process has been
shown to involve the CME pathway, which is in the case of growth cone repulsion and attraction is negatively regulated by Ca^{2+} signals [222–224]. Interestingly, at early developmental stages, macropinocytosis-like bulk endocytosis functions as the primary endocytic pathway for rapid retrieval of PM at axonal growth cones. This form of endocytosis requires RAC1 and the pinocytic chaperone Pincher [225]. Additionally, axon guidance and growth cone turning rely upon endocytosis for receptor trafficking [226].

For instance, chemorepulsion in the growth cone is controlled by synaptobrevin 2-dependent CME pathway (likely involving clathrin adaptors CALM and/or AP180), which is required for the SEMA3A-dependent signaling [227–229]. CME has also been shown to regulate the asymmetric distribution of β1-integrin receptors in the growth cone upon myelin-associated glycoprotein (MAG)-induced chemorepulsion [230], whereas the localization of WNT receptor Frizzled 3 at filopodia tips of commissural axonal growth cones has been shown to require the rapid ARF6-mediated endocytosis [231]. WNT signaling pathway in growth cones can also be directly regulated by the AP-2-dependent CME, as it has been shown for the WNT receptor Frizzled 4, whose internalization depends on the interaction of AP-2µ subunit with WNT pathway component Dishevelled [232]. Endocytic adaptor NUMB via its interaction with CRM2 and AP-2 regulates the CME of L1 at axonal growth cones and promotes axonal growth [233]. Neuronal polarization during development is also regulated by endocytosis, which helps to sort and deliver proteins destined for the axon or the dendrite. For instance, polarized localization of Synaptobrevin 2/VAMP2 and NAV1.2 in axons is achieved following their selective endocytosis from dendrites [234,235], whereas dendritic retention of glutamate receptors is achieved by their selective retrieval from the axon [236]. Blocking endocytosis causes a loss of somatodendritic polarity, likely as a result of missorting of dendritic cargo to the axon due to their decreased retrieval from the axonal PM [236].

**Endocytosis function in mature neurons**

The research of the last two decades has been especially productive regarding the identification of endocytosis function during presynaptic neurotransmission in mature neurons, which has been described in detail in several recent reviews [69,237–241] (Fig. 3). In brief, during chemical neurotransmission, SVs elicit a postsynaptic response by fusing with the presynaptic PM and releasing their neurotransmitter content into the synaptic cleft. It is suggested that during this process, a SV undergoes a full collapse, consequently losing its molecular identity [242,243]. To maintain the constant availability of functional SVs, neurons capitalize on CME and CIE pathways, although the exact contribution of these two pathways to presynaptic neurotransmission is currently debated [87,244]. CME operates at synapses to allow selective internalization of PM-localized SV proteins, followed by their sorting and incorporation into a newly generated SV [237]. Neuronal activity is correlated with a transient rise in the number of clathrin-coated endocytic intermediates, while SV proteins, including vesicular glutamate transporter (VGLUT) 1 [245], synaptotagmin 1 [246–248], synaptobrevin 2/VAMP2 [201,249], and SV glycoprotein 2A (SV2a) [250], are the major cargo of clathrin-coated vesicles isolated from nerve terminals [251,252]. Since in non-neuronal cells, CME is a slow process with a lifetime of 60–90 s, clathrin coat assembly at synapses can occur either directly on the PM [43,238,253–255] or at PM-derived endosomes [79,256,257]. The initial retrieval of SV membranes can also occur via the CIE pathway, active during moderate synaptic activity [75,79,107,258] and, depending on the strength of stimulation, takes hundreds of milliseconds (e.g., ultrafast CIE endocytosis [72]) to several seconds for completion [75,107,258]. In highly active neurons, a CIE mode called activity-dependent bulk endocytosis (ADBE) becomes active. ADBE shares a similarity with macropinocytosis by retrieving larger pieces of the presynaptic membrane (> 80 nm) [259]. The fact that clathrin and clathrin-binding adaptors are crucial for the regulation of SV function in neurons is supported by multiple studies indicating defects in SV biogenesis at synapses lacking CLC [134], AP180 [201,260,261], CALM [262], DAB [263], Epsin 1 [264], EPS15 [265] AP-2 [136,254,266,267], and AP-3 [268]. Neurons also use endocytic proteins involved in CME for rapid clearance of SV release sites during the neurotransmission, as indicated by experiments performed in Drosophila DAB mutants and mice lacking ITSN1 and AP180 [188,263,269]. Loss of CME proteins typically results in altered synaptic responses during sustained activity, as it has been shown using murine KO models of SYNJ1 [270], endophilin [137], dynamin 1 [130], amphiphysin [271], and BIN1 [272]. Interestingly, during intense neuronal activity, synapses can also bypass the requirement of dynamin and clathrin for the SV formation [273], although the molecular mechanism behind this phenomenon remains elusive. Endocytosis in neurons closely intersects with the autophagy pathway, which is supported by the fact that neuronal autophagy is directly regulated by
several players of the endocytic machinery, whose localization is synapse-enriched. These include regulators of SV recycling, such as AP-2 [136], endophilin A [274,275], and SYNJ1 [274] (for review, see [237]).

Mature neurons, like all other cells, employ endocytosis to regulate the PM content and control the initiation of signaling cascades in time and space. For instance, CME is crucial for the insertion and internalization of neurotransmitter receptors, such as GLUA1, GLUA2, and GLUA3 subunits of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors (AMPARs) [276–280], and GABAA receptors [281–283], while caveolin-dependent CIE endocytosis has been suggested to regulate the turnover of dopamine D1 receptor [284] and the localization of N-methyl-D-aspartate (NMDA) receptors subunits GLUN1, GLUN2, and GLUN2B to postsynaptic lipid rafts [285]. CME is also believed to act as a predominant endocytic pathway for the internalization of BDNF-bound TRKB receptors in neurons [8,286–288], although the involvement of CIE and macropinocytosis has also been described [136,289,290]. Following the endocytosis at distal axons, activated TRK complexes are internalized into a so-called ‘signaling endosome’, an organelle of endosome/amphisome-like identity, which continues to signal moving in a microtubule-mediated manner to the cell body [288,291–295]. Via its noncanonical function, endocytosis contributes not only to the internalization of activated TRK complexes into signaling endosomes but can also regulate their intracellular trafficking (for more details please see [237]). For instance, in primary mouse neurons, BDNF/TRKB complexes are internalized independent of AP-2, but their transport in signaling endosomes requires the association of AP-2 α subunit with autophagy modifier LC3 and the Dynein/
Dynactin subunit p150Glued [136]. An additional function of AP-2 in neurons involves the postendocytic regulation of BACE1 trafficking and degradation to prevent amyloidogenic processing of APP [296].

The cellular basis of learning and memory requires endocytosis to maintain the long-term changes at synapses during long-term potentiation (LTP) and long-term depression (LTD) [297]. For instance, the activity-dependent reduction and enhancement of AMPARs during LTD and LTP at the synapse are regulated by the imbalance of CME and exocytosis, respectively [298]. Clathrin core machinery is abundant at dendritic spines, where it is proposed to regulate the endocytosis of AMPARs during the LTD [299,300]. During the LTP, clathrin-dependent endocytosis may also contribute to AMPAR recycling for their subsequent insertion into the postsynaptic membrane [301]. Additionally, dampening of synaptic responses in response to hormones, neurotransmitters, or sensory signals also requires CME to regulate a process known as homologous desensitization [302,303]. During homologous desensitization, β-arrestin recruitment to activated (continuously or repeatedly stimulated) G protein-coupled receptors (GPCRs) at the PM promotes the functional uncoupling of activated receptors from their heterotrimeric G proteins. Internalization of β-arrestin-bound GPCRs prevents further stimulation of G proteins and is mediated by β-arrestin interaction with clathrin and AP-2 [304–306].

In contrary to the well-studied role of the CME, and increasing evidence of CIE pathways operating in neurons, the neuronal role of macropinocytosis remains vaguely defined. Macropinocytosis-like uptake has been suggested to function during axonal injury in vitro and in vivo [307], as well as to be involved in the propagation of neurotrophic aggregates, such as amyloid-β or α-synuclein in the brain [308]. Neuronal macropinocytosis is also suggested being a primary route for the entry of several viruses infecting the brain [309,310]. A recent report shows that macropinocytosis regulates presynaptic BMP-dependent synaptic development in Drosophila [311], while an earlier study suggested that bulk membrane retrieval at retinal bipolar cells might occur by a mechanism similar to macropinocytosis [312]. Constitutive AMPAR endocytosis has also been described to be clathrin- and dynamin-independent and requires GTPase RAC1 [278,313]. The fact that macropinocytosis is pivotal for the neuronal function is supported by genetic screens, identifying mutations in RAC1-effector alsin2 (ALS2) [314] and γPKC (a neuron-specific member of the classical PKC) as causes for a number of juvenile recessive motor neuron diseases [315–317] and spinocerebellar ataxia 14 [318], respectively. Finally, a combination of calcineurin- and dynamin 1-dependent macropinocytosis and CME operates to main the neurotransmission at the neuromuscular junction, and these endocytic processes are disturbed in patients with spinal muscular atrophy [319,320].

Other functions of endocytosis machinery in mature neurons might include the regulation of the neuropathic pain response [321], control of dendrite growth, arborization and pruning [136,322–325], dendritic spine morphogenesis [326], establishing of axon-dendrite polarity [327], and synaptogenesis [328–330].

### Endocytosis function in glial cells

Glia cells are non-neuronal cells in the CNS, which fulfill essential functions in regulating immune response [331], neurodegeneration [332], neurodevelopment [333] myelination [334], and synaptic plasticity [335,336]. Compared to neurons and neuronal precursors, we know significantly less about the roles of endocytosis in glia cells. Early ultrastructural work identified the presence of caveolae and clathrin-coated pits in developing rat astrocytes [337] and subsequent work implicated these pathways in the regulation of astrocyte physiology (Fig. 4). For instance, the endocytosis in astrocyte endfoot protrusions regulates the uptake of nutrients from blood endothelial cells. This process is independent of clathrin and dynamin and is regulated by intracellular Ca²⁺ concentration [338]. Endocytosis in astrocytes is also crucial for the recycling of glutamatergic synaptic-like microvesicles, proposed to mediate the interbrain communication upon Ca²⁺-triggered release [339]. Endocytosis could also directly contribute to the internalization of VGLUT 1–3 in a small set of astrocytes [340]. Clathrin-independent, Cav1-dependent endocytosis of megalin receptor regulates the astrocytic uptake of albumin, which promotes the synthesis of neurotrophic factor oleic acid [341]. In addition, CME-dependent endocytosis of the p75 receptor is used by astrocytes for the extracellular clearance of the BDNF precursor released upon the neuronal activity, thus regulating the BDNF spatial and temporal viability in the brain [342]. Endocytosis can also directly contribute to BDNF signaling in astrocytes by promoting the actin-mediated uptake of plasminogen [343]. CME- and actin-mediated uptake of amyloid-β might also be crucial in astrocytes to counteract the pathophysiology of Alzheimer’s disease [344,345]. The regulator of the innate immune response Toll-like receptor 3 also undergoes endocytosis in astrocytes; although the precise pathway remains to be investigated [346]. Finally, a new study highlights...
the role of CME in the maintenance of astrocytic intracellular ion homeostasis, where it regulates lysosome function and biogenesis [68].

Several reports are directed to the roles of macropinocytosis and phagocytosis in microglia cells, which are considered as ‘macrophages’ of the brain [347]. Microglia cells use these forms of endocytosis to engage in the noninflammatory clearance of apoptotic cells and cell debris [348], for the uptake of exosomes [349], and the clearance of amyloid-β [350,351] or SOD1 [352] aggregates. Microglial endocytosis of α-synuclein might also involve clathrin [353], although there are recent studies challenging this view by suggesting that microglia ingest and sequester α-synuclein into autophagosomes, independent of endocytosis or phagocytosis [354]. Interestingly, the astrocytic uptake of α-synuclein might be mediated by a different endocytosis pathway, involving dynamin 1 and the direct trafficking of α-synuclein in route to lysosomes [355]. To perform the aggregate removal, microglia cells also use a novel form of receptor-mediated endocytosis, termed LANDO (LC3-associated endocytosis) [356]. This pathway requires the association of autophagy modifier LC3 with amyloid-β containing RAB5- and clathrin-positive endosomes. Uptake of fibrillar amyloid-β 1–42 in microglia cells can also require the CME and the action of CD14 and Toll-like receptor 4 [357]. Endocytosis is also vital in oligodendrocytes, where it regulates the trafficking of myelin proteins, including proteolipid protein (PLP), MAG, and myelin-oligodendrocyte glycoprotein (MOG) [358,359]. Endocytosis of these proteins follows different routes, where MAG and MOG are internalized via CME, while PLP is taken up by a CIE cholesterol-dependent pathway. Interestingly, CIE-dependent PLP delivery to late endosomes/lysosomes is decreased upon brain maturation, where cAMP-dependent neuronal activity increases PLP levels on the PM, thus promoting axon myelination [360]. Finally, similar to newborn neurons, glial cells, including oligodendrocyte precursor cells (OPC) [361] and microglia [362], also migrate to reach their last destination, although relatively little is known about the mechanisms guiding these movements. A recent study shows that OPCs use receptor-
mediated endocytosis to regulate the levels of proteoglycan NG2, whose asymmetric localization is crucial for the OPC asymmetric cell division [363].

Concluding remarks

The last two decades were incredibly productive with respect to the identification of brain-specific functions of the endocytic machinery. Endocytic pathways function in the brain to regulate the differentiation and migration of neuronal cells during development and in adulthood, to maintain neuron morphology and sustain neurotransmission, as well as to direct the neurotoxic aggregates to lysosomes for degradation. Additionally, several noncanonical functions of endocytic machinery in the brain have been recently identified (Table 1). These include functions of endocytic proteins in the autophagy pathway [136,364], regulation of the degradation of amyloidogenic pathway components [296,365], and mitotic spindle organization [118–121]. Thus, it is not surprising that multiple associations between genes encoding endocytic proteins and a plethora of neurodevelopmental, neuropsychiatric, and/or neurodegenerative diseases have been reported (for review, please see [237,366–368]). How precisely dysfunctions in endocytosis machinery cause neurological defects in humans is a matter of further studies, which we believe are crucial to provide the groundwork for the identification of new therapeutic targets in neurological diseases.

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Table 1. Noncanonical functions of endocytic proteins in the brain. Summary of currently identified noncanonical functions of endocytic proteins in different cell types in the brain. Cell types in which no functions have been reported are marked with an interrogation sign (?). Several noncanonical roles of endocytic proteins have been discovered in the last years, revealing a whole new array of different unexpected functions, especially in cell division and trafficking.

| Protein     | Brain cell type       | Function                                                                 |
|-------------|-----------------------|--------------------------------------------------------------------------|
| Dynamin 2   | NPCs                  | Cytokinesis [126–128] ?                                                  |
|             | Migrating neurons     | ?                                                                        |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
| Clathrin    | NPCs                  | Stability of kinetochore fibers and spindle morphology [117–121] ?       |
|             | Migrating neurons     | ?                                                                        |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
| AP-2        | NPCs                  | Interaction with mitotic checkpoint kinase BubR1 [122] ?                  |
|             | Migrating neurons     | ?                                                                        |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
| Endophilin A| NPCs                  | ?                                                                        |
|             | Migrating neurons     | ?                                                                        |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
| SYNJ1       | NPCs                  | ?                                                                        |
|             | Migrating Neurons     | ?                                                                        |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
| CALM        | NPCs                  | ?                                                                        |
|             | Migrating Neurons     | ?                                                                        |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
| ITSN1       | NPCs                  | ?                                                                        |
|             | Migrating Neurons     | Reelin signaling and neuronal migration [191]                           |
|             | Mature neurons        | ?                                                                        |
|             | Glial cells           | ?                                                                        |
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Conflict of interest
The authors declare no conflict of interest.

Author contributions
SC-P and NLK cowrote the manuscript and designed the figures.

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