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Review

Is Stroke a Neurodegenerative Condition? A Critical Review of Secondary Neurodegeneration and Amyloid-beta Accumulation after Stroke

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Abstract: Stroke-induced secondary neurodegeneration (SND) refers to the progressive and inexorable loss of tissues at sites connected to area damaged by the initial infarction. SND has been consistently observed to occur in humans and rodents after stroke. Intriguingly, stroke-induced SND shares a number of striking similarities to other neurodegenerative diseases such as Alzheimer's disease, most notably with respect to the significant accumulation of the neurotoxic protein amyloid-β. Together, this observation and others (progressive neuronal loss and neuroinflammation) suggest the possibility that *stroke may induce a neurodegenerative condition*. Certainly, this is supported to some degree by the relatively high incidence of dementia after stroke. We begin this review by addressing the available research on human and rodent SND pathology after stroke. We next consider amyloid-β in the context of SND. We discuss what amyloid-β is, how is it made, and introduce some caveats on how amyloid-β measurements should be interpreted. In summary, we conclude that there is now robust pre-clinical evidence demonstrating the presence of amyloid disturbances at sites of SND after stroke. We find, however, that the human literature on the topic is more limited and further work is warranted. While the understanding of amyloid disturbances

remains inconclusive in human studies, stroke clearly lead to the development of a neurodegenerative-like condition at the sites of SND, with prominent features such as death of neurons and gliosis.

Keywords: Amyloid-beta; aggregation; secondary neurodegeneration; stroke; thalamus; Pittsburgh compound B

1. Introduction

Deficits in motor function and cognition after ischemic stroke are caused by the loss of brain tissue at the occlusion site. Critically, tissue death within the central nervous system does not stop at the border of the infarct and penumbral territories. Although, less researched, death of tissue at the infarction site triggers an insidious and apparently inexorable process known as secondary neurodegeneration (SND). SND involves the progressive death of regions that are anatomically connected to the infarction site but are often quite distal and can, in the short term at least, retain normal vascular supply [1,2]. SND has been consistently observed in clinical neuroimaging studies and in pre-clinical studies at the cellular level (see Table 1). Increasingly, it appears that sites of SND share many pathophysiological of common neurodegenerative diseases, including disturbances in amyloid-β (see Table 2). This observation is of particular interest, given that risk of dementia or cognitive decline is recognised to be dramatically elevated after stroke [3,4].

Given the progressive nature of SND, the presence of pathophysiological features such as altered levels of amyloid-β, and the increased risk of cognitive decline and/or dementia suggest the possibility that stroke initiates a neurodegenerative condition. The major highlight of this review is to specifically consider the presence of amyloid-β and its potential involvement in the SND pathology after stroke. Amyloid-β has already been extensively characterised for its involvement in Alzheimer's disease (AD) [5]. The role of amyloid-β in AD, however, continues to undergo continual expansion and revision (reviewed in [6–12]). In part this is because amyloid-β possesses a molecular structure that allows it to assume a large variety of configurations within the central nervous system, each of which appears to result in quite distinct biological effects [13,14].

This issue of specificity with respect to configuration state of amyloid-β is not simply academic matter for those concerned with SND after stroke. There have already been several studies to investigate changes in amyloid-β in the brain after stroke, the results of which show low or limited levels of alignment with each other [15–21]. In part, this misalignment may be attributable to which forms of amyloid-β are being measured and reported on. Failure to recognise this fact may lead to incorrect conclusions being drawn about the significance of amyloid-β over the course of recovery. As such, we will begin this review by giving a brief highlight addressing the basic processes of amyloid-β production, before moving to address the technical approaches used to measure it. We will

follow this with an overview of stroke-induced neurodegeneration with a focus on the thalamus and explore the findings from these studies that related to amyloid-β. The overall focus of this review is to conclude whether stroke is a neurodegenerative condition.

2. The Synthesis and Conformational States of Amyloid-β

Amyloid-β is a peptide of 36 to 43 amino acids and is usually produced in all neurons through sequential proteolytic processing of APP, by β-secretase and γ-secretase. Within the literature there are two primary monomeric amyloid-β isoforms; amyloid-β-40 (Aβ40) and amyloid-β-42 (Aβ42) [9]. Amyloid-β monomers have the propensity to self-assemble into soluble low molecular weight oligomers that can exist in several forms (e.g. dimer, an assembly of 2 monomers, trimer, an assembly of 3 monomers and so on). These low molecular weight oligomers can then form misfolded oligomers (known as "nuclei"), which will increase in size to form soluble high molecular weight oligomers (e.g. dodecamers also known as Aβ*56 [22]), and eventually continue to aggregate to form into insoluble amyloid fibrils (also known as beta-sheets) that deposit in the brain to yield dense core plaques (contain clumps of amyloid fibrils and other substances) (see Figure 1) [14].

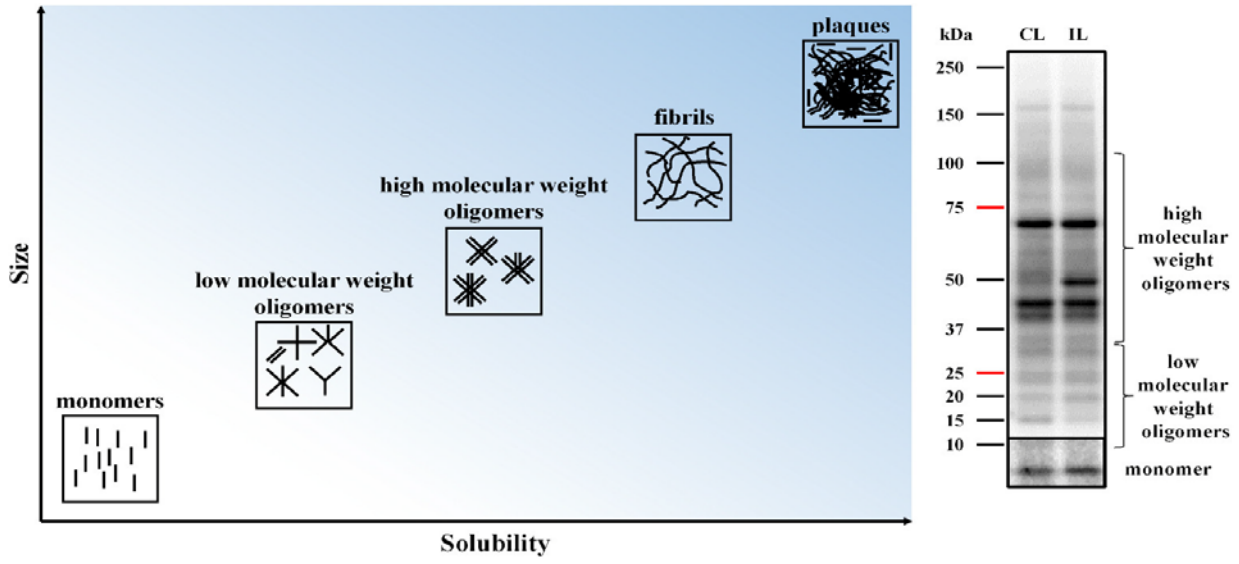

Figure 1. The conformational states of amyloid-β. Left panel, amyloid-β monomers self-assemble into low molecular weight oligomers, which increase in size to form higher molecular weight oligomers, and eventually continue to aggregate to form fibrils that deposit within the brain, ultimately yielding dense core plaques. As the amyloid-β aggregates from monomers to plaques, the conformation size increases and the solubility decreases. Right panel, provides an example of the change in oligomerisation status of amyloid-β within the stroked brain. Oligomerisation has been detected using western blotting, comparing amyloid-β within the contralateral (CL) and ipsilateral (IL) thalamus at 6 weeks after stroke. Amyloid-β antibody (D3D2N, #15126,

Cell Signaling Technology) detected soluble amyloid-β monomers (~5 kDa), low molecular weight oligomer (10–30 kDa) and high molecular weight oligomers (30–100 kDa).

The aggregation of amyloid-β and the eventual formation of plaques in the brain of AD patients has led to the development of the "amyloid hypothesis" [23]. This hypothesis simply holds that the overproduction, decreased clearance and/or enhanced aggregation of amyloid-β disrupt cellular functioning. While emphasis has been placed on dense core amyloid plaques as a primary driver of pathology in the context of AD, emerging literature has indicated that soluble amyloid-β oligomers, rather than the monomers or insoluble fibrils, may be responsible for the cellular pathology [6–8]. The soluble amyloid-β oligomers have been shown to permeabilize both cell and mitochondrial membranes and, therefore responsible for calcium dysregulation, membrane depolarization, and impairment of mitochondrial functions [24]. The soluble amyloid-β oligomers have also been shown to inhibit long-term potentiation in the hippocampus and, therefore, induce synaptic dysfunction [25].

3. Detection and Measurement of Amyloid-β

The accumulation of amyloid-β in brain tissue has commonly been investigated using histological stains such as Congo Red and Thioflavin T [26]. The original usage of these stains was to identify *amyloid fibrils and plaques in vivo* and to study amyloid-β aggregation process *in vitro*. Congo Red and Thioflavin T bind to beta-sheet-rich-amyloid fibrils and undergo spectral shifts to produce fluorescent signals. These stains, however, are not perfectly specific for the detection of other amyloid-β configurations including monomers and soluble oligomers. Therefore there are limits on how generalizable negative results using the stains are to lower molecular weight amyloid-β structures [27].

A more specific and comprehensive way to distinguish different forms of amyloid-β is through the use of amyloid-β antibodies [14]. These antibodies are used immunohistochemically on fixed brain tissue to visualise the distribution and localization of different amyloid-β species. Further, these antibodies have been used with biochemical assays on tissue lysates (such as brain extracts) for the quantitative detection and/or identification of specific amyloid-β species. For instance, antibody-dependent enzyme-linked immunosorbent assay provides information on the levels of specific amyloid-β isoforms and the presence of oligomers, but not specific size. These antibodies have also been used with western blotting to detect the presence of specific amyloid-β oligomers according to size (see Figure 1) [13,14].

Another approach used to study accumulation of amyloid-β in non-invasive imaging studies is the Pittsburgh compound B (PiB). [^{11}C]PiB (PiB is labelled with radioactive carbon 11) is injected intravenously and is then used in combination with positron emission tomography (PET) to detect cerebral amyloid-β plaques. [^{11}C]PiB was first used for imaging AD patients, which exhibited marked retention of [^{11}C]PiB in regions of the brain known to contain large number of amyloid

deposits in AD [28]. [^{11}C]PiB has now also been used to detect the amyloid-β accumulation in other neurodegenerative conditions (reviewed in [29]), including stroke [4,18,20,30]. *It should be noted that [^{11}C]PiB is recognised to have particularly high binding affinity for amyloid fibrils found in dense core plaques but low binding affinity to soluble oligomers or non-fibril amyloid-β forms* [31]. Therefore, [^{11}C]PiB and like Congo Red and Thioflavin T are limited in their ability to detect amyloid-β monomers and soluble oligomers. As such, there is a need to exert caution when interpreting positive and negative signal using [^{11}C]PiB, Congo Red and/or Thioflavin T. Often a combination of antibody-based assays would be required to obtain the most optimal information.

4. Neurodegeneration and Stroke

The typical features of neurodegenerative diseases are characterised by the selective and progressive neuronal loss, synaptic alterations and neuroinflammation (in the form of reactive astrogliosis and microgliosis) (reviewed in [32,33]). Another primary histopathological characteristic of neurodegenerative diseases is the presence of cerebral deposits of misfolded protein aggregates, such as amyloid-β (reviewed in [34]). For example, AD is characterised by neuronal loss, extracellular plaques comprising aggregated amyloid-β protein and intracellular neurofibrillary tangles generated by hyperphosphorylated forms of the microtubule-binding protein, tau [5]. Neurodegenerative diseases and stroke are classically characterised in different neurological disorders. They are viewed to be phenotypes of very different forms of neurological disorders; neurodegenerative diseases as a progressive neuronal loss and stroke as an acute vascular injury.

Although stroke is not widely recognised as a neurodegenerative condition, reports of ongoing degenerative changes in remote distal sites of the brain after the initial infarction have long been recorded. Degeneration distal to the infarction site has been most consistently observed in the thalamus. Thalamic disturbances have been shown to emerge within weeks of infarction, irrespective of the occlusion type and persist for several years after stroke using CT [35], MRI [36–38], DTI [38–40] and PET [41–43] after MCA infarction in humans. In experimental models thalamic degeneration has also been observed after MCA occlusion [44–48] or photothrombotic (PT) somatosensory cortex occlusion [49–51]. The most dominant histopathological feature of stroke-induced thalamic SND is neuronal loss concomitant with intense glial disturbance (see Figure 2). Table 1 summarizes neuroimaging and histological features of thalamic SND after stroke.

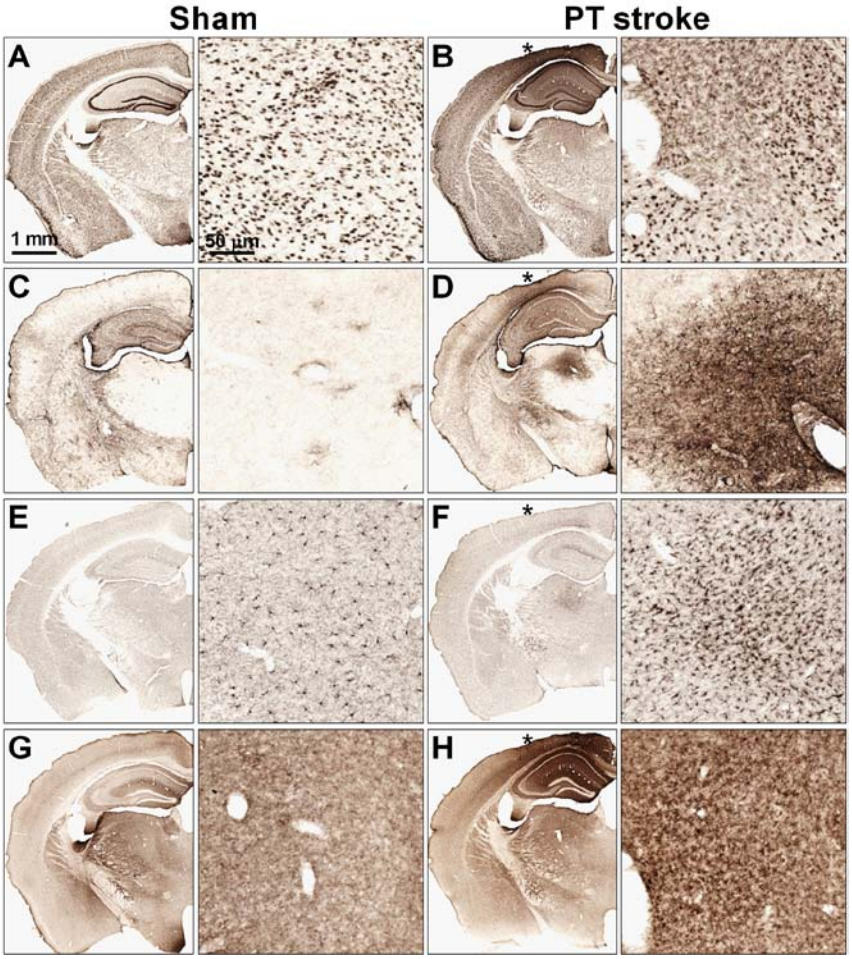

Figure 2. Typical features of thalamic SND at 6 weeks after PT somatosensory cortex occlusion. Immunohistochemistry staining of (A, B) NeuN, a marker for mature neurons, (C, D) GFAP, an astroglial cytoskeletal marker, (E, F) Iba1, a microglial specific cytoskeletal protein marker and (G, H) accumulation of amyloid-β. Scale bars represent 1 mm in low magnifying images and 50 µm in high magnifying images. The infract hemisphere is identified with asterisks (*).

5. The Accumulation of Amyloid-β in Stroke-induced Thalamic SND

As mentioned in the previous section, neurodegenerative diseases are characterised by loss of neurons and malformation of protein conformations in distinct brain regions leading to distinct functional deficits defining clinical presentations. It has been suggested that ischemic brain damage can induce accumulation of amyloid-β in the human brain [16,30], and has been further supported by rodent studies describing the accumulation of amyloid-β in thalamic SND after MCA stroke or PT stroke [15,17,21]. There is, however, some inconsistency between these rodent, human [18,20] and non-human primate [19] findings.

Only a few human studies have attempted to directly investigate the accumulation of amyloid-β at sites of thalamic SND after stroke. Amongst the first, was a large post-mortem study of 484 patient brains with cerebrovascular lesions [16]. The cerebrovascular lesions were classified as intra- or extra-axial and ischemic or haemorrhagic. Fixed post-mortem brain sections within the parietal cortex and thalamus from non-affected side lacking infarcts were immunohistochemically labelled with amyloid-β, Aβ40 and Aβ42. Amyloid-β accumulation was detected in the parietal cortex of 168 (34%) subjects and in the thalamus of 120 (25%) subjects.

Recently, three studies, to our knowledge, have examine amyloid-β after ischemic stroke using PET imaging of [^{11}C]PiB. The first study by Ly et al. examined the accumulation of [^{11}C]PiB within the peri-infarct region of 21 patients within 30 days after stroke [18]. The authors identified that [^{11}C]PiB retention in the peri-infarct region was higher relative to the contralateral hemisphere. No differences in [^{11}C]PiB retention were observed elsewhere in the brain. The second study by Liu et al. examined global cerebral accumulation of [^{11}C]PiB and the association of amyloid-β accumulation with cognitive changes over time [30]. The study involved 72 patients with cognitive impairment after stroke. The baseline cognitive assessment was performed on the patients at 3 to 6 months after stroke and the patients returned for annual follow-up over 3 years. [^{11}C]PiB PET scanning was performed only once at 11.6 ± 7.4 months post baseline cognitive assessment. The authors observed that not all patients presented with high levels of [^{11}C]PiB retention. There was, however, a robust and statistically significant positive correlation between higher levels of [^{11}C]PiB retention and cognitive decline. The third study by Sahathevan et al. examined [^{11}C]PiB accumulation in 47 ischemic stroke patients [20]. The primary comparison involved comparing [^{11}C]PiB retention in the peri-infarct region to a reference region in the undamaged hemisphere, no differences were observed between these regions. Further, the authors observed no evidence of [^{11}C]PiB accumulation in the ipsilateral hemisphere of 21 patients over 18 months after stroke. Sahathevan et al. attributed the misalignment of their results to those reported earlier by Ly et al. to a number of issues including the use of a larger sample size and more accurate definitions of the infarct and non-infarcted zones. On the basis of these results the authors proposed that ischemic stroke does not result in increased or sustained accumulation of amyloid-β within the brain.

In rodent studies, the accumulation of amyloid-β is particularly common and robust finding, especially within the thalamus [15,17,21]. Amyloid-β immunostaining in the thalamus often appears as a diffuse aggregation at 1–6 weeks (see Figure 2) and over time transforms into dense deposits at 9 months after stroke. Recently, our research team has reported the first evidence that the accumulation of amyloid-β observed within the thalamus after stroke is associated with enhancement of soluble amyloid-β oligomers [21]. Further, this enhancement of soluble amyloid-β oligomers is associated with loss of neurons within the thalamus after stroke [21], suggesting that the low and high molecular weight soluble amyloid-β configurations may be responsible for the cellular pathology [6–8]. Together, the rodent studies demonstrate that stroke can trigger amyloid deposition,

most likely through interference in amyloid production or clearance pathways. Table 2 summarizes clinical and pre-clinical observation of amyloid-β accumulation in stroke-induced thalamic SND.

The pathology of SND after stroke typically develops in delayed manner similar to other neurodegenerative diseases, thus offering a wider therapeutic time window for stroke recovery. Over the last few years much effort has been made in pre-clinical/rodent studies targeting the "amyloid hypothesis" to ameliorate stroke-induced SND. These pre-clinical studies suggest that elimination of the neurotoxic protein itself may alleviate the loss of neurons leading to improvement in functional outcomes [52–55] and vice versa [21,56]. Table 3 summarizes pre-clinical studies on interventions which modulate thalamic amyloid-β accumulation after stroke.

6. Summary and Future Perspectives

There is now robust neuroimaging and histological data to support the existence of SND after stroke in both human and animal studies (see Table 1). *The histopathological features of stroke-induced thalamic SND, the persistent loss of neurons and intense glial disturbance, clearly suggest that stroke triggers a neurodegenerative condition.* In terms of linking this neurodegenerative response to the disturbances of amyloid-β, the rodent studies are very consistent, with accumulation of amyloid-β routinely being observed (see Table 2). Human studies of amyloid-β disturbances, however, are currently few in number. We could identify only four clear human studies examining amyloid-β levels after stroke, with one utilising histological staining [16] and the other three based on PET with [^{11}C]PiB [18,20,30]. Aho et al. and Liu et al. reported clear signs of amyloid-β disturbance, whereas, Sahathevan et al. reported no obvious changes. Together, it would be unreasonable to propose that these human studies be taken to support or oppose significant disturbances in amyloid-β. Certainly, larger longitudinal studies are warranted. It is important to recognise that the [^{11}C]PiB signal only provides information on amyloid fibrils and plaques, and not on non-fibril based amyloid-β disturbances [31] (see Figure 1). This is relevant as an increasing number of studies suggest that the non-fibrillar forms of amyloid-β, rather than the fibrils and plaques, are responsible for the disruption of cellular functions [6–8]. This is further supported by observation in rodent studies from our research team that accumulation of soluble amyloid-β oligomers is associated with neuron loss within the thalamus 6 weeks after stroke [21].

In summary, this short review has attempted to provide evidence that stroke is associated with neurodegeneration, characterised by progressive neuronal death accompanied by intense glial disturbance, and these phenomena occur in both humans and rodents. There is robust evidence concerning the presence of amyloid-β at sites of stroke-induced SND in rodent studies and preliminary evidence of same effect in human studies. Further, pre-clinical studies suggest that amyloid-β can be modulated at sites of stroke-induced SND to provide therapeutic benefit (see Table 3). More evidences from further clinical studies, especially non-human primate studies, are needed. This may provide a potential therapeutic direction for future clinical studies.

Table 1. Clinical and pre-clinical studies investigating neuronal death and gliosis in thalamic SND after stroke.

Species	Stroke location/model	Method of measurement	Conclusion	Reference
Human	MCA infarction	CT	Thalamus gradually reduced in size 3–12 months after stroke.	Tamura et al., 1991
Human	MCA infarction	MRI	Hypointensity in the thalamus at 1–12 months after stroke.	Ogawa et al., 1997
Human	MCA infraction	MRI	Hypointensity in the thalamus 6 weeks after stroke.	Nakane et al., 2002
Human	MCA infraction	DTI	Thalamus increased in mean diffusivity at 3 and 6 months after stroke.	Buffon et al., 2005
Human	MCA infraction	DTI	Thalamus progressively increased in mean diffusivity at 1–6 months after stroke.	Herve et al., 2005
Human	Corona radiata infarction	MRI and DTI	Thalamus increased in mean diffusivity at 12 weeks after stroke.	Li et al., 2011
Human	MCA infarction	PET with [^{11}C]PK11195, a marker of activated microglia	Persistently, increased tracer binding, suggesting microglia activation in the thalamus at 2 weeks–6 months after stroke.	Pappata et al., 2000
Human	MCA infarction	PET with [^{11}C]PK11195	Thalamus increased in tracer intensity (microglia activation) at 28–150 days after stroke.	Gerhard et al., 2005
Marmoset	MCA occlusion	Neuronal tracer injection	Decreased of labelled neurons in the thalamus at 45 days after stroke.	Bihel et al., 2010
Rat	MCA occlusion	Area analysis with computer digitizer	Progressive shrinkage of the thalamus at 2 weeks–6 months after stroke.	Fujie et al., 1990
Rat	MCA occlusion	Silver staining and IHC with GFAP, a marker of astrocytes	Loss of neurons and activation of astrocytes detected in the thalamus at 3 and 6 weeks after stroke.	Iizuka et al., 1990
Rat	MCA occlusion or PT parietal cortex	Nissl staining and IHC with GFAP and OX-42 (a marker	Enhanced glial activation detected in the thalamus at 1 day after stroke, preceded the reduction of neurons at 2 weeks.	Dihne et al., 2002

	occlusion	for microglia)		
Rat	MCA occlusion	MRI and IHC with NeuN, GFAP and OX-42	Persistent hypointensity in the thalamus from 7 until 24 weeks after stroke. Neuronal loss in the thalamus accompanied by strong glial reactivity at 3 to 24 weeks after stroke.	Justicia et al., 2008
Mouse	Somatosensory cortex ablation	Nissl staining and IHC with GFAP	Persistently, enhanced astrocytes activation detected in the thalamus at 2 days and up to 60 days after stroke, preceded the degeneration of neurons.	Ross & Ebner, 1990
Mouse	PT somatosensory cortex occlusion	IHC with NeuN and various markers of microglia/monocytes (Iba1, CD11b, CD68 and MHC-II)	Loss of neurons concomitant with intense activation of microglia/monocytes in the thalamus at 4 weeks after stroke.	Jones et al., 2015
Mouse	PT somatosensory cortex occlusion	IHC with GFAP	Astrogliosis in the thalamus at 4 weeks after stroke.	Patience et al., 2015

CT, computed tomography; DTI, diffusion tensor imaging; IHC, immunohistochemistry; MRI, magnetic resonance imaging; PET, positron emission tomographic; PT, photothrombotic.

Table 2. Clinical and pre-clinical observation of amyloid-β pathology in stroke-induced thalamic SND.

Species	Stroke location/model	Method of measurement	Conclusion	Reference
Human	Cerebrovascular lesion (location not mentioned)	IHC with amyloid-β (Dako, M0872)	Amyloid-β accumulation was detected in the parietal cortex of 168 (34%) subjects and in the thalamus of 120 (25%) subjects (total 484 subjects).	Aho et al, 2006
Human	Ischemic stroke (location not mentioned)	PET with [^{11}C]PiB	[^{11}C]PiB retention in the peri-infarct, but not the thalamus within 30 days after stroke (total 21 subjects).	Ly et al., 2012
Marmoset	MCA occlusion	IHC with amyloid-β (Covance, 6E10)	Accumulation of amyloid-β in the peri-infarct and substantia nigra, but not the thalamus at 45 days after stroke (4 stroke subjects versus 2 controls).	Lipsanen et al., 2013
Rat	MCA occlusion	IHC with amyloid-β (Signet, Aβ3–16)	Transformation of diffuse amyloid-β staining at 1 week after stroke to dense plaque-like deposits in the thalamus at 9 months.	van Groen et al., 2005
Rat	MCA occlusion	IHC with amyloid-β (Covance, Aβ3–16)	Accumulation of amyloid-β in the thalamus at 26 weeks after stroke.	Makinen et al., 2008
Mouse	PT somatosensory cortex occlusion	IHC and western blotting with amyloid-β (Cell signalling Technology, #15126)	Accumulation of amyloid-β which is associated with enhancement of soluble amyloid-β oligomers in the thalamus at 6 weeks after stroke.	Ong et al., 2016

Table 3. Pre-clinical studies on interventions which modulate thalamic amyloid-β accumulation after stroke.

Species	Stroke model	Intervention	Conclusion	Reference
Rat	MCA occlusion	Single oral administration of γ-secretase inhibitor, DAPT (50 mg/kg), at 3 days after stroke	DAPT treatment was associated with reduction of thalamic amyloid-β accumulation, attenuation of neuron loss and glial activation and improvement of sensory function at 7 days after stroke.	Zhang et al., 2011
Rat	MCA occlusion	Daily oral administration of calcium channel blocker, beprildil (50 mg/kg), at 2 days after stroke	Beprildil treatment decreased soluble amyloid-β 40 and 42 in the thalamus and improved sensorimotor function at 29 days after stroke.	Sarajarvi et al., 2012
Rat	MCA occlusion	Single intraventricular injection of autophagy inhibitor, 3-MA (600 nm), at 1 day after stroke	3-MA treatment decreased thalamic amyloid-β accumulation and neuron loss at 7 and 14 days after stroke.	Zhang et al., 2012
Rat	MCA occlusion	Single intraarterial infusion of BMMSC (1×10^6) at 2 or 7 days after stroke	BMMSC treatment elevated thalamic amyloid-β accumulation and impaired sensorimotor function.	Mitkari et al., 2015
Mouse	PT somatosensory cortex occlusion	Chronic restraint stress at 3 days after stroke	Chronic stress exacerbated thalamic amyloid-β accumulation and neuron loss at 6 weeks after stroke.	Ong et al., 2016

DAPT, N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester; 3-M, 3-methyladenine; BMMSC, bone marrow-derived mesenchymal stem cells.

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Conflicts of Interest

All authors declare no conflict of interest.

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