Vascular contributions to cognitive impairment and dementia (VCID): Topical Review of Animal Models

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Introduction

Cerebrovascular disease and Alzheimer's disease (AD) lesions are very common in older people, and accumulate with age. Cerebrovascular lesions can directly reduce cognitive status: vascular dementia is the second most-common cause of clinical dementia after AD. In addition, cerebrovascular lesions worsen the impact of AD and other dementia pathologies, and may contribute to AD aetiology. This spectrum is reflected in the concept of Vascular contributions to Cognitive Impairment and Dementia (VCID)[1].

There are numerous vascular pathologies underlying VCID[2-4]. The most prevalent is cerebral small vessel disease (SVD), or arteriolosclerosis, in small arteries (outer diameter up to ~ 200μm) that supply deep nuclei and deep white matter areas in the human brain[2, 3, 5, 6]. Parenchymal lesions associated with SVD vasculopathy are small focal infarcts ("lacunes"), diffuse white matter lesions (WML), and microhemorrhages[3, 4, 6]. Other VCID-related vascular pathologies include microatheroma, venous collagenosis and cerebral amyloid angiopathy (CAA)[1, 3, 6].

The limitations of animal models for VCID are well-known[1, 7, 8]. Experimental species differ from humans in terms of lifespan, relative white matter abundance, large artery dimensions (Figure 1) and in size and morphology of deep penetrating arteries (Figure 2). Nevertheless, animal paradigms provide valuable insights into mechanisms, progression and possible therapies in VCID. All experimental use of animals for human health-related research carries ethical responsibilities, and must be governed by internationally-agreed Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines (www.nc3rs.org.uk/arrive-guidelines). Here we update a previous systematic review of VCID-relevant models[8] (Online Supplement, please see http://stroke.ahajournals.org) and summarize instructive examples (Table 1).

**** Figures 1 and 2 near

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Hypoperfusion: rats and mice

Bilateral surgical ligation of the common carotid arteries (2VO) in rats remains the most frequently-used model[8] (see Online Supplement). Bilateral carotid artery stenosis (BCAS) in mice, using metal coils to narrow the arteries by 50%, produces a less-severe, chronic global hypoperfusion[29, 30]. BCAS mice develop some white-matter damage, increased BBB permeability and cognitive impairment[29, 31]. F18-FDG-PET indicates a decrease in hippocampal glucose utilization 6 months post-BCAS. In the radial maze and Barnes maze tasks, working memory was impaired at 30 days. Impaired reference memory was also detected at 5-6 months post-surgery[8, 9].

After six months of stenosis the animals display significantly (30%) reduced fractional anisotropy on diffusion tensor imaging in white matter areas[9]. Histologically, they exhibit thickened basement membrane collagen IV (relative to one month post-BCAS and sham-operated animals)[9] and hippocampal atrophy with pyknotic and apoptotic cells from 6-8 months post-surgery[29]. An unexpected finding in BCAS mice is the incidence at six months of subcortical haemorrhagic lesions, detected on MRI and confirmed histologically[9]. The haemorrhagic lesions, and an astroglial response with unusual distribution of aquaporin-4, suggest a pathological process additional to global hypoperfusion[9, 30].

In order to produce more gradual CBF reduction, ameroid micro-constrictor cuffs filled with casein (which swells on absorbing water) are placed around the carotid arteries of rats[10]. In rats gradual bilateral occlusion (2VGO) over 2-3 days leads to comparable CBF reduction and white matter damage, with lower mortality and hippocampal neuronal death, relative to

the standard 2VO rat model[8, 10]. 2VGO in hypertensive (SHR) rats produced a gradual reduction in global CBF (to 68% of baseline values, after 7 days) and cognitive impairment in the Y-maze[12]. Mice with an ameroid constrictor placed on one common carotid artery and a microcoil causing 50% stenosis on the other ("ACAS" mice) exhibit subcortical infarcts in addition to diffuse white matter damage[11]. ACAS mice exhibited gradual reduction of CBF over 28 days, and multiple infarct damage in subcortical regions ipsilateral to the ameroid constrictor cuff, observed in 81% of the mice[11]. At day 28 post-surgery, ACAS mice showed significant decrease in spatial working memory[11].

Hypoperfusion: baboons

In adult baboons (*Papio anubis*; age 12 years or more) occluding one vertebral and both internal carotid arteries (termed three vessel occlusion; 3VO), led to a severe hypoperfusion state[13]. Activation of microglia was marked at 3 days post-occlusion, and plasma extravasation at 7-14 days, both being resolved by 28 days. From 7 days post-occlusion these animals developed progressive white matter pallor and vacuolation in the corpus callosum, deep subcortical and periventricular white matter areas, with some demyelination, up to sacrifice at 28 days[13]. While a primate surgical model poses substantial logistic challenges, data from a human-like experimental species with extensive white matter are uniquely valuable[7, 32, 33]. For VCID-relevant research, it is notable that ageing baboons exhibit both β-amyloid and tau neuropathology.

Hypoperfusion paradigms in relation to clinical SVD and VCID

Regional CBF in white-matter is universally low across species (figure 1). This is generally considered to explain the white matter predilection for diffuse hypoperfusion lesions. In

human brain the deep subcortical white matter is supplied by the distal fields of deep penetrating medullary arteries (length 50 mm or more) arising from the leptomeningeal branches of the anterior, middle and posterior cerebral arteries. Thus, even under normal circumstances this deep white matter is subject to relatively low perfusion pressure. Though there are some anastomoses between these vessels[34], an episode of profound global hypoperfusion (eg. acute ICA occlusion) causes white matter infarcts in a characteristic deep or internal borderzone distribution[35]. Experimental induction of abnormally-low perfusion pressure in an animal (e.g. 2VO or 3VO models) would be expected to cause ischaemic white matter damage with a similar pattern.

A caveat is that pathogenesis of WML in these hypoperfusion models is very different from human SVD. The majority of WML and lacunes in humans are thought to arise as a direct result of local small vessel wall changes[3] not from embolic events or episodes of global hypoperfusion. Hence, while experimental proximal large vessel occlusion will cause white matter changes, the distribution of lesions is likely to be more confined and stereotyped, and other features contributing to the local milieu in chronic hypertensive arteriopathy, such as blood brain barrier (BBB) dysfunction, are likely to be different in such models, or absent. Further, any vascular adaptions such as ischaemic preconditioning[36] are unlikely, except where occlusion is more gradual (e.g. 2VGO).

Hypertensive rodents with co-morbidities

Spontaneously hypertensive stroke prone rats (SHRSP) develop severe hypertension from 9-12 weeks of age and typically exhibit stroke lesions at 9-12 months, with 90% mortality by 12 months of age[8]. Stroke lesions are frequently haemorrhagic in nature and are unpredictable in timing, severity, location and behavioural outcome. In the absence of co-morbidities,

stroke-free SHRSP exhibit little white matter change on MRI or histologically[14, 37, 38]. In SHRSP subjected to unilateral carotid artery occlusion (UCCAo), then a combination of low-protein, high salt diet (so-called "Japanese permissive diet", JPD) and NaCl (1%w/v)-supplemented drinking water, diffuse WML were seen on MRI[14]. These were accompanied by impaired performance in the Morris water maze (MWM). Histologically there was loss of myelin, signs of inflammatory response and matrix metalloproteinase-mediated BBB disruption[14]. While mature oligodendrocytes were depleted in white matter of SHRSP, oligodendrocyte progenitor cells paradoxically increased in density[14, 37]. The WML were accompanied by hypoperfusion, determined by arterial spin labelling MRI, and reduced brain tissue pO_2 measured by electron paramagnetic resonance[15]. Hypoxia-induced HIF-1α, activating MMP-2, may be the pathway for BBB disruption. The antibiotic minocycline has both anti-inflammatory and anti-apoptotic activity. Young SHRSP were treated with this drug (50mg/kg ip, every 2 days) for 9 weeks, following the UCCAo surgery and transfer to JPD. Minocycline-treated animals showed an impressive protection from WML on MRI, modest improvement in the MWM, and increased lifespan, relative to vehicle-treated animals[16].

While SHRSP develop severe hypertension, milder chronic hypertension is induced by supplementing drinking water with the NOS-inhibitor L-NAME[39], or chronic infusion of angiotensin II by minipump[40]. Mice receiving a "sub-pressor" infusion of angiotensin II develop mild hypertension (MABP 90 mmHg, relative to 70 mmHg in saline-infused controls)[40]. In addition to vascular actions, sub-pressor concentrations of the hypertensive agent may have direct effects on neural organization and metabolism.

Hyperhomocysteinemia in mice and rats

Elevated plasma concentration of the non-essential amino acid homocysteine, termed hyperhomocysteinemia (HHCy), is a risk factor for VCID[41]. In wildtype mice a diet deficient in three B-vitamins (B6, B9-folate and B12) resulted in HHCy within 10 weeks, accompanied by reduced capillary density in brain tissue and impaired performance in MWM[17]. The same dietary regime also exacerbated cognitive impairment in APP transgenic mice[18].

Maintaining wildtype mice for 12 weeks on a diet enriched for the HCy precursor methionine, in addition to B6/B9/B12-defficiency, resulted in plasma [homocysteine] in the range 70-90 µmol/l[19] classified as "moderate" HHCy in mice[19, 41] (physiological range for plasma [homocysteine] in healthy mice and humans: 5-10 µmol/l). These mice exhibited cognitive impairment on the two-day radial arm water maze, increased metalloproteinase (MMP2, MMP9) activity in brain tissue and small focal cerebral haemorrhages[19]. The methionine-enriched, B6/B9/B12-defficient diet was also applied to dual mutant APP/PS1 mice[20]. In these animals, cerebral microhemorrhages (evident on MRI and histology) were accompanied by redistribution of β-amyloid deposits from brain parenchyma to the microvasculature[20].

In rats B9-folate deficiency alone was sufficient to induce HHCy and cognitive impairment, and to reduce cerebral blood volume and reactivity measured by absolute, non-invasive near infra-red spectroscopy[42]. While the molecular mechanism of HHCy-induced VCID is unclear, the locus of pathology appears to be vascular rather than neuronal[41].

Animal models of Blood-brain barrier dysfunction

Pdgfr$^{-/-}$ mice deficient in pericytes, the contractile cells that ensheath capillary vessels, showed progressive BBB breakdown from one month of age, with increasing extravasation of plasma proteins in the hippocampus and cerebral cortex. This was accompanied by reduced

capillary density and age-dependent reduction in baseline CBF and response to a vasogenic stimulus (whisker twitch)[43]. By 16 months of age the mice exhibited pronounced neuronal loss within the hippocampus, accompanied by impaired performance in a simple assay of learning (novel object recognition task)[43].

APOE genotype is a risk factor for sporadic AD. The *APOE ε4* allele increases risk, possibly via a toxic effect of the APOE ε4 gene product, or via loss of physiological APOE function. In an elegant series of target replacement (TR) studies, mice lacking native *ApoE* expressed the human alleles *APOE 2, 3 or 4*, under an astrocyte-specific promoter. TR mice carrying only the *APOE* ε4 allele (like *ApoE*$^{-/-}$ null mice) exhibited enhanced BBB permeability that was evident by two weeks of postnatal age[25, 26]. This was dependent on MMP9 activity, induced via the pro-inflammatory cytokine cyclophilin-A[25]. None of these changes was evident in *APOE*2 or *APOE3* TR mice. *APOE*4 TR mice exhibited worse spatial memory relative to age-matched *APOE*3 TR animals at older ages (12, 24 months) but also in young adulthood (3 months)[27, 28].

Regional CBF was much reduced in the *APOE4* TR or *ApoE*$^{-/-}$ null animals at 9 months of age. CBF could be restored and was at normal levels in double knockout animals, lacking *ApoE* as well as the gene for cyclophilin-A[25]. These well-defined transgenic animal systems allow specific biochemical pathways to be explored. The gene product of *APOE3* binds to the membrane transporter LRP1, and this supresses the harmful effects of cyclophilin-A on MMP9 activation and BBB breach[25]. These experiments also suggest that the harmful effect of *APOE4* is loss of function, rather than a toxic action of the *APOE4* gene product. A functional APOE and LRP1 transport system stimulates clearance of amyloid peptides and possibly other brain parenchymal debris. Further, when *APOE4* TR mice are crossed to the APP transgenic mouse models of amyloid deposition, CAA is significantly increased, suggesting a potential role for ApoE4 in the vascular accumulation of amyloid[44].

Another molecular participant in β-amyloid clearance from brain tissue is PICALM, a phosphoinositide binding protein associated with clathrin that is required for endocytosis and internalisation of cell surface receptors. PICALM interacts with endothelial LRP1 to mediate β-amyloid clearance from brain tissue[45]. Heterozygous *Picalm*$^{+/-}$ mice, expressing sub-physiological levels of PICALM protein in brain endothelium, exhibited increased β-amyloid neuropathology and some cognitive impairment, assessed with measures of nest-building and burrowing[45]. PICALM has emerged as a candidate in genome wide association studies (GWAS) for AD, suggesting a key role in the pathogenesis of AD and dementia[46].

CADASIL and CARASIL mice

CADASIL and CARASIL are rare monogenic forms of SVD, leading to early-onset VCID. In CADASIL the underlying gene is *NOTCH3* and in CARASIL the gene is *HTRA1*.

Notch3^{R169C} transgenic mice have 4-fold overexpression of CADASIL-associated mutant Notch3. These mice exhibit defective CBF reactivity from 5 months of age, reduced CBF from 12 months and progressive WML from 18 months[21]. The main WML were microvacuoles within the myelin sheath, suggested to reflect defective ion-water homeostasis[24]. There was no apparent loss of oligodendrocyte density and axons were intact[24]. The extracellular matrix proteins vitronectin and TIMP-3 accumulated in the vascular GOM deposits that are characteristic of CADASIL. Double-transgenic mice that express CADASIL-causing *Notch3* mutations, in addition to being heterozygous null for vitronectin, exhibit rescue from WML at 12 to 20 months of age, but not rescue of impaired CBF. Stroke lesions have not been reported for these mice (up to age 24 months). Another transgenic strain has recently been reported[22], carrying the human genomic *NOTCH3* sequence. Knock-in Notch3Arg170Cys mouse models, with a mutation in the endogenous

Notch3 gene[23], developed a CADASIL-like vessel pathology and, in addition, some incidence of parenchymal lesions (from 20 months of age)[23]. Micro-infarcts, micro-haemorrhages and behavioural motor deficits were seen in a minority (up to 12%) of these mutant mice up to age 13 months[23].

HTRA1 encodes a secreted serine protease that is involved in TGFβ signalling. CARASIL-causing mutations result in loss of HtrA1 activity. Brain tissue from *Htra1*$^{-/-}$ null mice, and fibroblasts from CARASIL patients, exhibited reduced TGFβ signalling and dysregulation of an extracellular TGFβ-binding protein (LTPB-1) that is a novel HtrA1 target[47]. In brain tissue from *Htra1* null mice, LTBP1 levels were augmented and TGFβ signalling depressed[47].

Discussion

Co-morbid models

Greater understanding of interactions between risk factors, genotype and specific vascular lesions (Figure 3) may come from animals with multiple pathologies and/or co-morbidities. Examples are hypertensive rats with JPD diet and brain hypoperfusion[14, 16], or diet-induced HHCy combined with AD pathology[20]. In AD molecular understanding is more advanced than in VCID and transgenic AD models are well-established. VCID-AD overlap and interaction may therefore be explored using vascular challenges combined with brain-injected Aβ peptides[48] or in APP transgenic animals[30].

****** Figure 3 near***

Larger Species.

Larger animals (primates, dogs, sheep, swine) have longer natural life span than rodents, and offer valuable data relevant to the human brain gyrencephalic anatomy, abundant white-matter and arterial morphology (Figure 2), even though cohort sizes may necessarily be limited[13, 33]. They can be subjected to VCID-relevant risk factors (old age, hypertension, high-fat diet, physical exercise status). Rhesus macaques 20-30 years of age are considered analogous to older people 60-90 years of age[33]. Quantitative MRI of these animals shows a highly significant reduction in white matter volume with increasing age[33]. In old dogs a cognitive dysfunction syndrome, featuring some aspects of VCID, has been described[49]. Experimental sheep models have recently been developed to simulate acute ischemic stroke[50, 51]. Sophisticated cognitive testing paradigms are available for primates[32, 52]. By contrast, cognitive paradigms for large domestic species are currently rudimentary[53, 54].

A very small species: Zebrafish.

Perturbation of *FOXC1* (which encodes a forkhead-like transcription factor) in *Danio rerio* led to cerebral haemorrhages[55]. *FOXC1*. GWAS studies suggested possible linkage of the *FOXC1* locus with SVD phenotype (white matter hyperintensities). Suppression of *FOXC1* also affected PDGF signalling and CNS development[55]. The zebrafish offers a rapid screening platform for genetic alterations.

Summary

Animal models have great potential to increase our understanding of specific vessel pathologies, how these cause parenchymal lesions, how known risk factors influence vessel and parenchymal changes, and the mechanisms that link them all to VCID (Figure 3).

For example, transgenic animals permit well-controlled testing of molecular hypotheses regarding a functional pathway, such as ApoE-mediated clearance[25, 26, 43, 45]. "CADASIL mice" carrying *Notch3* mutations combine a known molecular cause with biologically-appropriate vessel pathology and parenchymal lesions reminiscent of human SVD[21-24]. The risk factor HHCy is induced by dietary manipulation in rodents, which exhibit vessel fibrosis, microhaemorrhages and cognitive deficits[17-20]. HHCy mice and rats offer a valuable platform for identifying the currently-unknown molecular targets of HHCy-related brain disease[41]. Diffuse WML can be induced in rodents following chronic hypoperfusion[9-12] and also in SHRSP with dietary and surgical co-morbidities[14, 16], in both conditions with some concomitant cognitive deficit. As noted, the vascular pathology in these animals is likely to differ from human VCID (Figure 3).

There are several directions for future progress. In our view experimental species with closer metabolic and immunological similarity to humans (primates, larger domestic species) will make pre-clinical testing of interventions more translational. Given the multi-factorial nature of the VCID spectrum, co-morbid animals may also accelerate discovery biology for VCID treatments. While the models discussed here clearly do not reflect the full pathogenic pathway of human disease (Figure 3) they represent a pragmatic test-bed for interventions[11, 12, 16]. VCID is a broad concept[1], and there is no one "optimal VCID model". We hope that this review will assist selection of experimental models most relevant to the aspect of VCID under study.

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Figure Legends

Figure 1. Lifespan and cerebral large artery diameter, white matter content and blood flow: comparison across species.

A, normal lifespan (open circles) and outer diameter of the middle cerebral artery just off the circle of Willis (MCA; filled circles, microns). Typical data for mouse (Ms), rat, cat, dog, monkey (Macaque) and human.

B, white matter volume as a fraction (%) of total cerebral volume (squares), global CBF (filled circles) and white matter CBF (WM; open circles). X-axis shows greatest whole brain width in coronal section (mm).

Figure 2. Deep penetrating arteries in rat, pig, monkey and human.

A, adult SHRSP male rat, age 8 months. Small penetrating artery within the caudate nucleus is labelled immunohistochemically for smooth muscle α-actin (brown, DAB chromagen).

B, young adult domestic pig, age 29 weeks. Small artery within subcortical white matter. Periodic acid-Schiff (PAS) stain labels connective tissue within the artery wall bright pink.

C, adult monkey, *Macaca mulatta* (archive material). Small penetrating artery in the caudate nucleus stained with phosphotungstic acid-haematoxylin (PTAH).

D, older human (male, aged 76 y) with severe small vessel disease. In small penetrating arteries within deep subcortical white matter, the basement membrane is labelled immunohistochemically for collagen-α1IV (brown). Note the endothelium (arrow) and an advential layer of collagen-α1IV (arrowheads).

Unpublished data (AHH). In all cases, nuclear chromatin is counterstained with haematoxylin (blue). Scale bars 20 μm.

Figure 3. Schematic for VCID pathogenesis.

Numerous risk factors, some of which are listed, impact on vessel and parenchymal changes, and also on the mechanisms that link these to each other and to VCID. In addition, rare monogenic mutations are causal, including *NOTCH3*, *HTRA1* and *COL4A1/COL4A2* (the genes encoding collagen-α1IV and collagen-α2IV).

Table 1. Overview of selected VCID-relevant models

Model	**Cognitive Impairment**	**Brain Pathology**	**Selected References**
Global hypoperfusion: rat 2VO, 2VGO; mouse BCAS, ACAS	Working memory deficits; later, RM deficits (MWM, Barnes maze, Y-maze)	Diffuse WML; some BBB deficit, microglial activation; micro-haemorrhages at 6 mo.	9-12
Global hypoperfusion: baboon 3VO	Not reported	Progressive, diffuse WML; transient microglial activation; transient global BBB opening	13
SHRSP, with JPD and UCCAo	Memory deficits (MWM)	Diffuse WML; neuroinflammation, BBB deficit	14-16
HHCy in mice, rats	Learning deficits (MWM)	Micro-haemorrhages; CAA	17-20
Notch3 transgenic mice	Not reported	Vessel fibrosis; later, WML; reduced CBF. No BBB deficit	21-24
ApoE deficient mice	Learning deficits (MWM, Barnes maze)	BBB deficit (from 2 weeks); CAA	25-28

Abbreviations: BBB: blood-brain barrier. BCAS: bilateral carotid artery stenosis. CAA: cerebral amyloid angiopathy. JPD: Japanese permissive diet. MWM: Morris water maze.

RM: reference memory. UCCAo: unilateral common carotid artery occlusion. 2VGO: two-vessel gradual occlusion. 3VO: three vessel occlusion.

SUPPLEMENTAL MATERIAL

Vascular contributions to cognitive impairment and dementia (VCID): Topical Review of Animal Models

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Supplementary Method

Search Strategy for systematic review. Using PubMed, we searched English language publications in the period 01/01/2010–31/01/2016 for the following terms: (brain OR cerebral) AND (cogniti* OR dement*) AND (Vascular OR cerebrovascular OR arteri*) AND (vivo OR rodent OR rat OR mouse OR murine OR rabbit OR gerbil OR hamster OR porcine OR swine OR cat OR feline OR dog OR canine OR primate OR monkey OR marmoset OR baboon).

This search yielded 238 hits, of which 33 were reviews. For the remaining 205 papers, abstracts were independently screened by two authors (JBM, AHH) and the following exclusion criteria applied: not an animal model; not an in vivo model; not an appropriate disease/injury model; review article, without original data; conference abstract or other non-peer-reviewed source. Conflicts (on 25 selections) were resolved by discussion. Additional hits were added from bibliographies of included papers, and review articles. A final list of 100 papers were selected (below). Compare with our previous systematic review[1].

Supplementary Results

Models retrieved by systematic review 2010-2016

Chronic hypoperfusion

Rat; bilateral common carotid artery occlusion (BCCAo); also referred to as two-vessel occlusion (2-VO)[2-38]

Rat; two vessel gradual occlusion (2-VGO)[39]; 2-VGO in SHR rats[40]

Rat; three vessel occlusion (3-VO)[41]

Mice; bilateral carotid artery stenosis (BCAS)[42-48]; BCAS in $ASK^{-/-}$ mice[49]; BCAS in mice with HHCy[50]

Mice; unilateral common carotid artery occlusion (UCCAo)[51, 52]; UCCAo with intra-gastric C. butyricum[53]

Baboons; 3-VO, 28 days[54]

Acute global ischaemia

Mice; transient BCCAo[55]

Hyperhomocysteinemia (HHCy)

Rats; dietary induction of HHCy[56-59]; high homocysteine and/or high cholesterol diet[60]

Mice; dietary induction of HHCy[61, 62]

Cystathionine beta-synthase deficient ($CBS^{+/-}$) mice [63, 64]

Diabetes mellitus-related changes and insulin/glucose control

Diabetic rats; streptazocin-treated[65]

Diabetic rats; obese-Zucker[66]; Otsuka Long-Evans Tokushima Fatty rats, with 2-VO[67]

Mice with CNS-restricted deletion of the insulin receptor substrate protein 2 (IRS-2)[68]

Hypertensive animals

Hypertensive rats (renal artery ligation)[69]

Hypertensive rats SHRSP[70-72]

Hypertensive rats SHR[73]

Hypertensive mice; NADPH oxidase subunit Nox2-deficent; aortic banding; dietary L-NAME[74]

Hypertensive mice; chronic administration of angiotensin II[75]

Endothelial NO synthase deficient, $eNOS^{+/-}$ mice[76]

With focal ischaemic lesions

Middle cerebral artery occlusion (MCAo), $P2Y_1$-null mice[77]

Mice; permanent single penetrating arteriole occlusion[78, 79]

Rats; micro-particle emboli (50-180 μm)[80]

Mice; multiple micro-infarcts induced by injection of cholesterol emboli (40-70 μm), in addition to unilateral internal carotid artery occlusion[81]

Vascular features of AD-relevant models

APP/PS1 transgenic mice; CAA, micro-hemorrhage[82]

APP transgenic mice (Tg2576 strain); with UCCAo[83]

Rat; intra-striatal injections of endothelin-1 (ET1) and β-amyloid[84]

Rat; β-amyloid i.c.v. injections in addition to 2-VO[85]

Tau transgenic mice (rTg4510 strain); vascular effects[86, 87]

Mice; Apoe-deficient, APOE2/APOE3/APOE4-expressing; CypA-defficient[88]

CADASIL and CARASIL-related mice

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Notch3 transgenic mice[89-92]

CADASIL Notch3 transgenic mice; with MCAo[93]

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) HtrA1 null mice[94]

Miscellaneous

Rats; alpha-adrenoceptor autoantibodies[95]

Senescence-accelerated mouse prone 8 (SAMP8) mice[96]

Rats; involuntary physical exercise[97]

Rats; long term (12 month) dietary ethanol and/or high dietary cholesterol[56, 98]

Mice; hippocampal C-reactive protein (CRP) injection[99]

Rats; vascular calcification (0.75% adenine)[100]

Mice; Endothelia-specific depletion of the transcription factor Serum Response Factor SRF[101]

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