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Cytochrome P450 eicosanoids and cerebral vascular function

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The eicosanoids 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs), which are generated from the metabolism of arachidonic acid by cytochrome P450 (CYP) enzymes, possess a wide array of biological actions, including the regulation of blood flow to organs. 20-HETE and EETs are generated in various cell types in the brain and cerebral blood vessels, and contribute significantly to cerebral blood flow autoregulation and the coupling of regional brain blood flow to neuronal activity (neurovascular coupling). Investigations are beginning to unravel the molecular and cellular mechanisms by which these CYP eicosanoids regulate cerebral vascular function and the changes that occur in pathological states. Intriguingly, 20-HETE and the soluble epoxide hydrolase (sEH) enzyme that regulates EET levels have been explored as molecular therapeutic targets for cerebral vascular diseases. Inhibition of 20-HETE, or increasing EET levels by inhibiting the sEH enzyme, decreases cerebral damage following stroke. The improved outcome following cerebral ischaemia is a consequence of improving cerebral vascular structure or function and protecting neurons from cell death. Thus, the CYP eicosanoids are key regulators of cerebral vascular function and novel therapeutic targets for cardiovascular diseases and neurological disorders.

Cerebral blood flow is controlled to provide overall adequate oxygenation to the brain through a complex interplay between cerebral blood flow 'autoregulation', to maintain a basal supply of oxygen to the brain, and 'neurovascular coupling', to increase blood flow to areas of the brain with increased neuronal activity (Refs 1, 2, 3, 4, 5, 6, 7).

Autoregulation is defined as maintenance of constant organ blood flow over a wide range of arterial pressures (Refs 8, 9, 10). Cerebral blood flow is autoregulated at arterial pressures from

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70 to 120 mmHg to ensure adequate oxygen delivery to the brain (Refs 8, 10). Myogenic regulation of precapillary blood vessels and metabolic regulation of organ blood flow are the two general mechanisms that contribute to autoregulation (Ref. 9). Myogenic response is defined as the constriction of small arteries and arterioles in response to an increase in transmural pressure. Cerebral arteries originating from the circle of Willis and pial arteries on the surface of the brain are highly myogenically active (Ref. 10). This myogenic response increases cerebral vascular resistance to minimise changes in blood flow and pressure to cerebral capillaries. Metabolic cerebral blood flow autoregulatory adjustments occur at the level of small precapillary arterioles (Ref. 10). Thus, autoregulation is provided by the myogenic and metabolic responses of cerebral arteries and arterioles, resulting in constant organ blood flow over a wide range of arterial pressures. Impaired autoregulation results in inappropriate blood flow to organs and increased transmural pressures at the level of the arterioles and capillaries. Although autoregulatory responses can initially adapt in disease states such as hypertension, autoregulation eventually becomes dysfunctional in these chronic pathophysiological states such as arterial hypotension, carotid stenosis or intracranial hypertension (Refs 3, 4). This impaired blood flow autoregulation over time contributes to vascular and organ damage associated with these disease states.

Neurovascular coupling (also known as functional hyperaemia) is a process whereby local neuronal activity leads to dynamic changes in cerebral blood flow. Neurovascular coupling requires dynamic regulation of glucose and oxygen levels to match metabolic demand in active regions of the brain (Refs 5, 7, 11). Experimental studies have determined that sensory activation results in increases in cortical cerebral blood flow within 1–2 s that reach a steady state by 5–10 s (Refs 5, 6, 7). Astrocytes have a pivotal role in this dynamic regulation of cerebral circulation (Refs 3, 5, 6, 7). Neuronal activity is transmitted by astrocyte cell signalling events that travel to astrocytic foot processes surrounding arterioles within the brain (Refs 6, 7, 11), which provide a venue for controlling vascular smooth muscle tone. This process results in increased cerebral blood flow to regions of the neuronal network with increased activity, while preventing a passive decrease in blood flow to other regions (Refs 5, 6, 7).

Interestingly, in numerous disease states impaired cerebral blood flow autoregulation and an altered neurovascular coupling are both evident (Refs 3, 4). Additionally, these interactions between cerebral blood flow autoregulation and dynamic changes in blood flow in response to neuronal activation remain poorly understood.

Metabolites of the arachidonic acid cytochrome P450 (CYP) pathway – epoxyeicosatrienoic acids (EETs) and 20-hydroxyeicosatetraenoic acid (20-HETE) – are produced by cerebral blood vessels, astrocytes and neurons, and have actions on the regulation of cerebral blood flow that position them as crucial regulators required for the interaction between autoregulation and neurovascular coupling (Refs 5, 6, 7). Overall, EETs have been demonstrated to be key mediators coupling neuronal activity and astrocytes to evoke cerebral arteriolar dilatory responses (Refs 5, 6, 7), whereas 20-HETE is a key contributor to the myogenic response and autoregulation of cerebral blood flow (Refs 2, 6, 7); however, many specific details of their roles in these processes remain to be explored. This review summarises recent findings on these CYP eicosanoids with regard to cerebral vascular function and the potential for manipulating the metabolites to provide protection to the brain in various pathological states.

Cerebral CYP metabolites

The eicosanoids EETs and 20-HETE are generated by the action of CYP enzymes on arachidonic acid in two distinct pathways: the CYP epoxygenase pathway generates EETs, and the CYP hydroxylase pathway generates 20-HETE (Fig. 1). CYP4A hydroxylase enzymes are responsible for cerebral vascular 20-HETE generation (Refs 12, 13). CYP4A3 is the major rat isoform expressed in cerebral circulation (Ref. 12); other CYP enzymes that could contribute to rat cerebral vascular 20-HETE generation include CYP4F isoforms, CYP4A1 and CYP4A8 (Refs 12, 14). CYP2C and CYP2J epoxygenase enzymes are primarily responsible for the generation of EETs in the brain (Refs 7, 15). These CYP epoxygenase enzymes have been localised to neurons and astrocytes in various regions of the brain (Refs 7, 15); interestingly,

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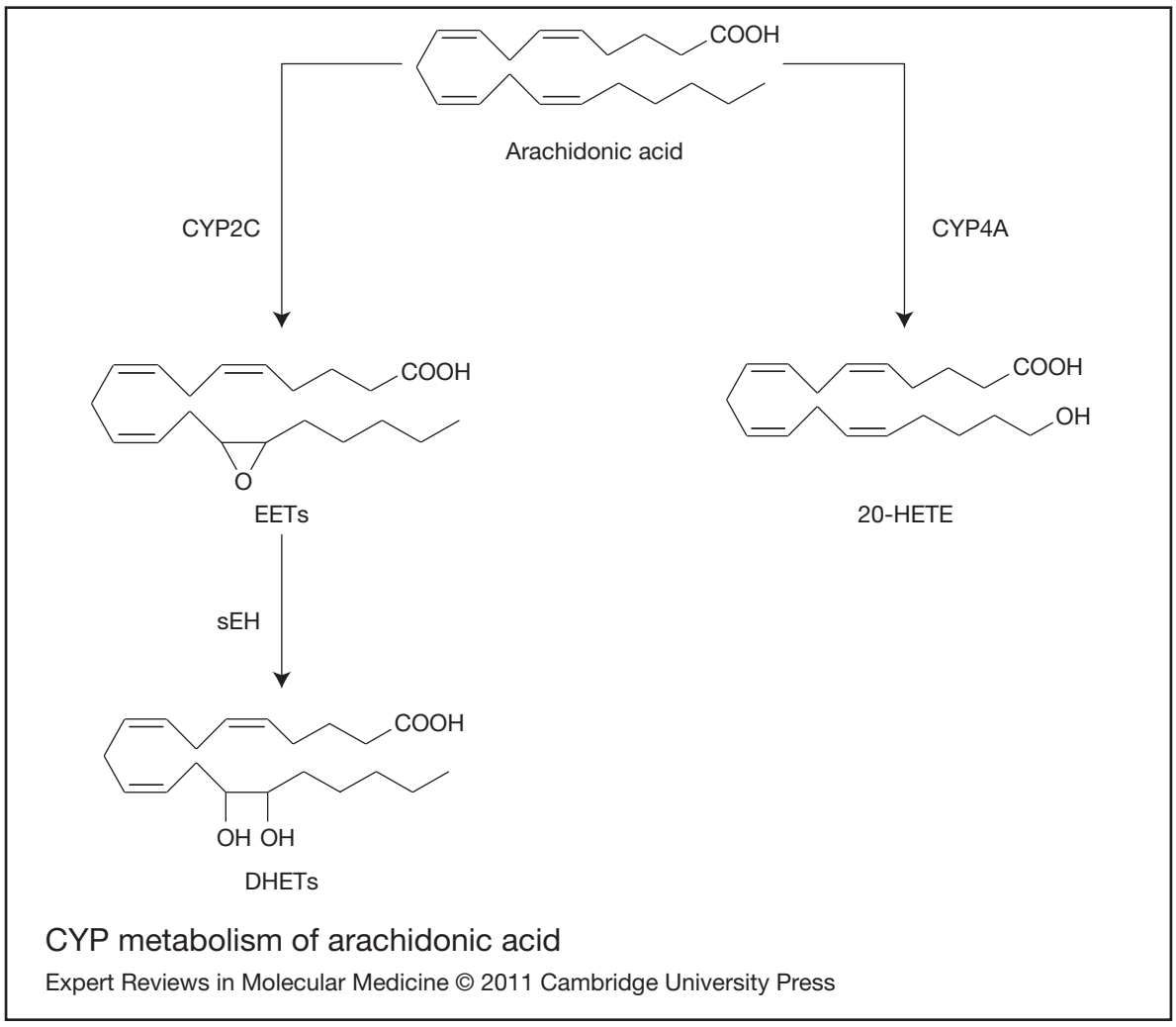

Figure 1. CYP metabolism of arachidonic acid. Arachidonic acid can be metabolised by CYP2C enzymes to generate EETs. EETs can be converted by sEH to the corresponding less active DHETs. CYP4A is a hydroxylase that converts arachidonic acid to 20-HETE. Abbreviations: CYP, cytochrome P450; DHET, dihydroxyeicosatrienoic acid; EET, epoxyeicosatrienoic acid; 20-HETE, 20-hydroxyeicosatetraenoic acid; sEH, soluble epoxide hydrolase.

there is limited experimental evidence that cerebral blood vessels show epoxygenase activity (Ref. 15). EETs are further metabolised by soluble epoxide hydrolase (sEH) into their less active diol, dihydroxyeicosatrienoic acids (DHETs) (Fig. 1). Neurons, astrocytes, oligodendrocytes, ependymal cells, endothelial cells and vascular smooth muscle cells have all been found to express sEH (Ref. 15).

CYP metabolites in neurovascular coupling

Neurovascular coupling is the result of neuronal activity in a specific region of the brain that culminates in a local increase in blood flow (Refs 5, 6, 7). The biological mechanisms responsible for this temporally and spatially coordinated coupling are complex and involve nitric oxide, CYP epoxygenases and K^+ channel activation (Refs 6, 7).

Nitric oxide does not appear to be an essential component because mice deficient in endothelial nitric oxide synthase (eNOS; encoded by *Nos3*) and neuronal nitric oxide synthase (nNOS; encoded by *Nos1*) have normal cerebral blood flow responses to whisker stimulation (Refs 6, 7). Other findings show that nitric oxide acts in a permissive manner to ensure that cGMP levels in vascular smooth muscle cells are at a level

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that allows for vasodilation by other mediators (Refs 3, 5, 6, 7).

Another key contributor to the functional hyperaemic response is CYP-derived EETs generated in astrocytes in response to release of glutamate by neurons (Refs 5, 6, 7). EETs generated by astrocytes can then act to open large-conductance Ca^{2+}-activated K^+ channels (K_{Ca}) on astrocytes and vascular smooth muscle cells, resulting in hyperpolarisation and vasodilation (Refs 6, 7). EET antagonists or EET synthesis inhibition can attenuate the increase in cerebral blood flow on activation of the cerebral cortex (Ref. 6).

The eicosanoid 20-HETE can also impact neurovascular coupling. 20-HETE does not have a great influence on the increase in cortical cerebral blood flow in response to whisker barrel stimulation in either rats or mice (Ref. 16); however, when nNOS is inhibited, 20-HETE exerts a greater influence on the functional hyperaemic response by diminishing the EET contribution (Ref. 16). Nitric oxide suppresses 20-HETE generation by binding to the CYP4A haem group to inhibit hydroxylase activity, resulting in facilitation of EET activation of K_{Ca} channels (Ref. 14). Taken together, 20-HETE and EETs influence neurovascular coupling and this is in part due to vascular interactions between these CYP metabolites.

CYP metabolites in autoregulation

With regard to cerebral blood flow autoregulation, previous studies have demonstrated that EETs can limit pressure-mediated vasoconstriction (Ref. 17). In support of this notion, enzymatic inhibitors of epoxygenase activity enhance arteriolar constriction when perfusion pressure is increased from 80 to 120 mmHg (Ref. 17). An interesting aspect of the interaction between EETs and 20-HETE in the functional hyperaemic response is that 20-HETE has been identified as an essential component of the myogenic response (Fig. 2) (Ref. 18). CYP hydroxylase inhibitors abolish arteriolar constriction in response to perfusion pressure (Refs 8, 14, 18). 20-HETE activation of the protein kinase C pathway appears to be a key cell signalling mechanism contributing to the myogenic response (Ref. 14).

CYP metabolites in cerebral vascular disease

Neurovascular coupling and cerebral blood flow autoregulation can be altered in pathophysiological states (Ref. 3). Hypertension is one such disease state, which can result in cerebral vascular remodelling, impaired endothelial function and impaired cerebral blood flow autoregulation (Refs 1, 2, 3). A decrease in the functional hyperaemic response to whisker stimulation has been observed in animal models of hypertension, and there is evidence that functional hyperaemic responses are altered in humans with hypertension (Refs 3, 16, 19, 20). Mouse models of Alzheimer disease demonstrate impaired neurovascular coupling and cerebral blood flow autoregulation: cerebral blood flow autoregulation is almost absent and functional hyperaemia is impaired (Refs 21, 22). Ischaemic stroke is also associated with impaired cerebral blood flow autoregulation and a reduced functional hyperaemic response (Refs 23, 24). These pathophysiological states demonstrate that impaired neurovascular coupling and vascular dysregulation can affect overall brain function. Interestingly, each of these disease states has impaired cerebral blood flow autoregulation and an altered functional hyperaemic response. The unique and complex interactions between functional hyperaemic responses, cerebral blood flow autoregulation and CYP eicosanoids are just beginning to be defined.

As mentioned, pathophysiological states such as hypertension, carotid stenosis or intracranial hypertension impair neurovascular coupling and cerebral blood flow autoregulation and decrease appropriate adaptation of cerebral myogenic tone (Refs 1, 3, 19, 20). A decrease in myogenic tone could possibly limit vasodilation during neuronal activation. In addition, increases in myogenic tone are associated with increases in 20-HETE generation that counteract the opening of vascular smooth muscle cell K_{Ca} channels (Refs 13, 18). Because increases and decreases in cerebral myogenic tone occur during the confounding issues associated with pathophysiological states, it has been difficult to assess the interaction between metabolic and autoregulatory control of cerebral blood flow. Dysregulation of EETs or sEH has the potential to be associated with impaired neurovascular coupling. Rat astrocytes express CYP2C11, which synthesises EETs, and in turn these can be degraded and inactivated by sEH localised in neurons and cerebral blood vessels (Refs 6, 7). Interestingly, an increase in CYP2C11 and EET production in astrocytes following intermittent

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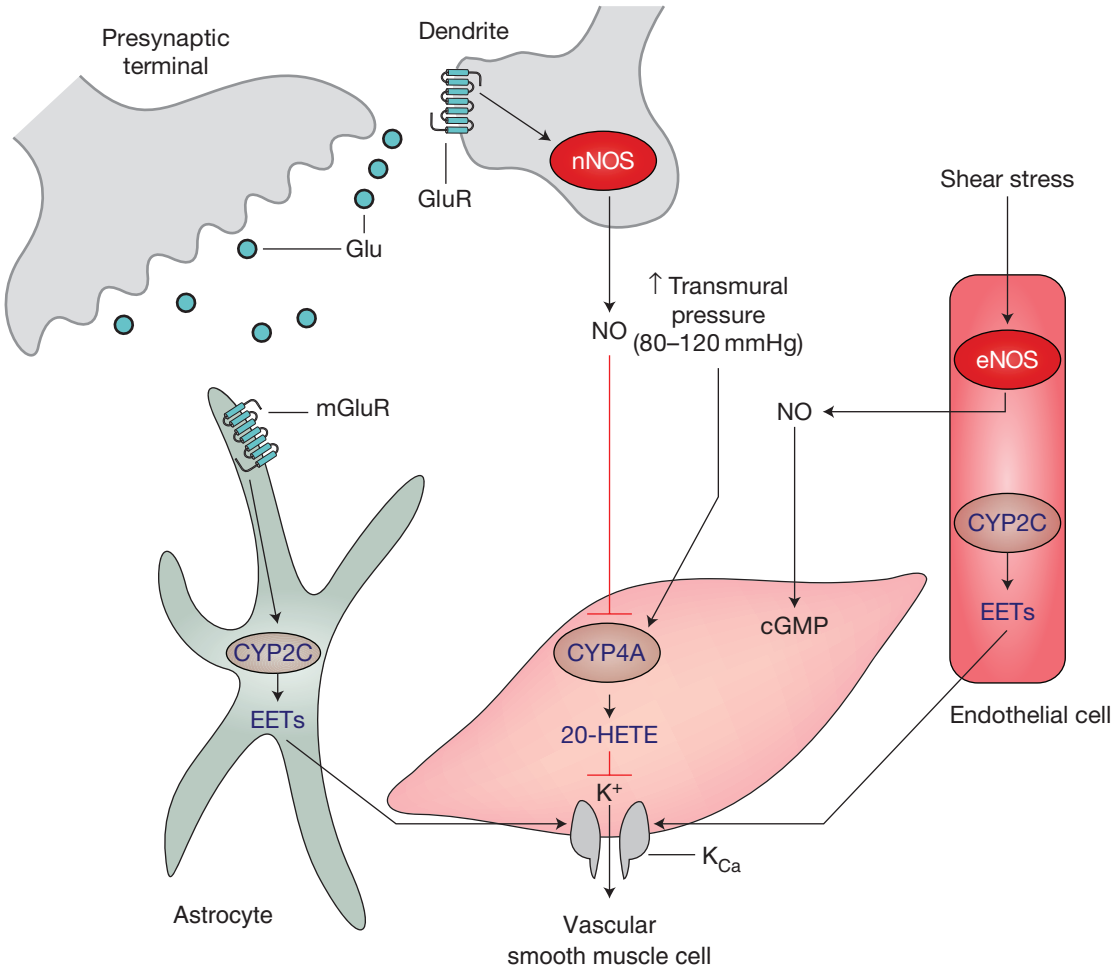

CYP eicosanoids in neurovascular coupling and cerebral blood flow autoregulation

Figure 2. CYP eicosanoids in neurovascular coupling and cerebral blood flow autoregulation. This simplified diagram indicates how CYP metabolites might link neural activity and haemodynamics to cerebral blood flow regulation. (Upper left) Neurovascular coupling involves presynaptic release of Glu, which acts on mGluRs on astrocytes and GluRs on dendrites. In astrocytes, this results in activation of CYP2C to generate EETs. In dendrites Glu increases neuronal nitric oxide synthase (nNOS/NOS1) to produce NO. NO can act on vascular smooth muscle cells to decrease CYP4A generation of 20-HETE. (Upper right) An increase in transmural pressure as occurs in the cerebral blood flow autoregulation myogenic response can increase 20-HETE production. In addition, shear stress can activate endothelial nitric oxide synthase (eNOS/NOS3) in endothelial cells to produce NO; this increases vascular smooth muscle cell cGMP, which results in vasodilation. Endothelial cells can also produce EETs; however, endothelial-derived EETs appear to play a lesser role in cerebral blood flow control compared to their role in other organs. (Lower centre) In vascular smooth muscle cells, EETs can activate large-conductance calcium-activated K^+ channels (K_{Ca}), resulting in vasodilation, whereas 20-HETE inactivates K_{Ca}. Abbreviations: CYP, cytochrome P450; EET, epoxyeicosatrienoic acid; Glu, glutamate; GluR, postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor; 20-HETE, 20-hydroxyeicosatetraenoic acid; mGluR, postsynaptic metabotropic glutamate receptor; NO, nitric oxide.

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hypoxia appears to confer a neural protective action (Refs 6, 7). Although the contribution of the CYP metabolites EETs and 20-HETE to the interaction between metabolic and autoregulatory regulation of cerebral blood flow is not completely defined, it is clear that pharmacological manipulation of these metabolites can have profound effects on the brain damage that occurs with cerebral ischaemia and stroke.

Cerebral ischaemia: stroke and CYP eicosanoids

Stroke is the third leading cause of death in the USA, and someone dies of stroke every three minutes. Of even more concern is the fact that stroke is the number one cause of serious, long-term disability in the USA (Refs 25, 26, 27). Haemorrhagic strokes are commonly associated with an aneurysm in the brain and account for a small percentage of all strokes. As such, there are limited data on the contribution of CYP-derived EETs and 20-HETE to haemorrhagic stroke; however, 20-HETE inhibition has potential therapeutic value for this stroke type. Ischaemic strokes or strokes caused by blood clots (thrombotic or embolic) account for 80% of all strokes (Refs 25, 26, 27). Because ischaemic stroke occurs along with a loss of cerebral blood flow regulation and is associated with cardiovascular diseases such as hypertension, manipulation of CYP-derived EETs and 20-HETE has potential for managing ischaemic stroke.

Protective role for EETs?

CYP-derived EETs are vasodilators, profibrinolytic, anti-inflammatory and angiogenic, and can match cerebral blood flow to increased neural activity and metabolic demand (Refs 7, 28, 29). Hence, increasing EETs has the potential to protect the brain from damage that occurs during and following a cerebral ischaemic event. Delivering EETs is impractical because, as fatty acids, they can rapidly bind to plasma proteins or be metabolised. The application of more metabolically stable and active EET agonists to treat animals has recently been successful (Refs 30, 31), but the pharmacological approach that has been widely used is to reduce the degradation of EETs by inhibiting sEH (Ref. 32).

Epidemiological data demonstrating an association of increased risk for ischaemic stroke in patients with a genetic polymorphism in *EPHX2*, the gene responsible for generating the sEH protein, support the notion that sEH inhibition could be beneficial for the treatment of stroke (Refs 33, 34). The *EPHX2* G860A polymorphism but not *CYP2J2*-50T allele frequency had a protective influence on ischaemic stroke in Chinese nonsmokers (Ref. 35), whereas homozygosity for the *EPHX2* K55R polymorphism conferred a higher risk for hypertension prevalence and increases the risk for ischaemic stroke in Swedish men (Ref. 36). In another study, three single-nucleotide polymorphisms identified in Caucasian Europeans in or near the *EPHX2* gene were associated with increased risk for ischaemic stroke (Ref. 37). However, a more recent report that genotyped participants in three Copenhagen studies failed to find a relationship between the *EPHX2* gene and risk for ischaemic stroke and other cardiovascular diseases (Ref. 38); thus, the risk for ischaemic stroke in humans with *EPHX2* polymorphisms requires additional evaluation in larger and more ethnically diverse populations.

Even though epidemiology studies in humans concerning sEH and risk for ischaemic stroke are somewhat divisive, inhibitors of sEH have been consistently demonstrated to decrease cerebral ischaemic injury in rats and mice (Refs 39, 40, 41, 42). The sEH inhibitor 12-(3-adamantan-1-yl-ureido)dodecanoic acid (AUDA) protects against cerebral ischaemia in spontaneously hypertensive stroke-prone (SHRSP) and Wistar–Kyoto (WKY) rats (Refs 39, 40). The SHRSP rat is an inbred strain that is derived from the SHR strain and is characterised by hypertension, vascular wall remodelling and reduced cerebral blood flow (Ref. 43). Cerebral haemorrhage or infarct occurs by five months of age in a majority of SHRSP rats (Ref. 43). Likewise, middle cerebral artery occlusion in young SHRSP rats results in a large area of infarct (50%) when compared with age-matched WKY rats (20%, Fig. 3) (Ref. 43). Chronic AUDA treatment in SHRSP rats decreased infarct size induced by middle cerebral artery occlusion even though blood pressure was not altered in this hypertensive animal (Refs 39, 40). Cerebral ischaemic–reperfusion injury in normotensive mice was also decreased by sEH inhibition (Ref. 42). Short-term sEH inhibitor treatment also protects the brain from cerebral ischaemic

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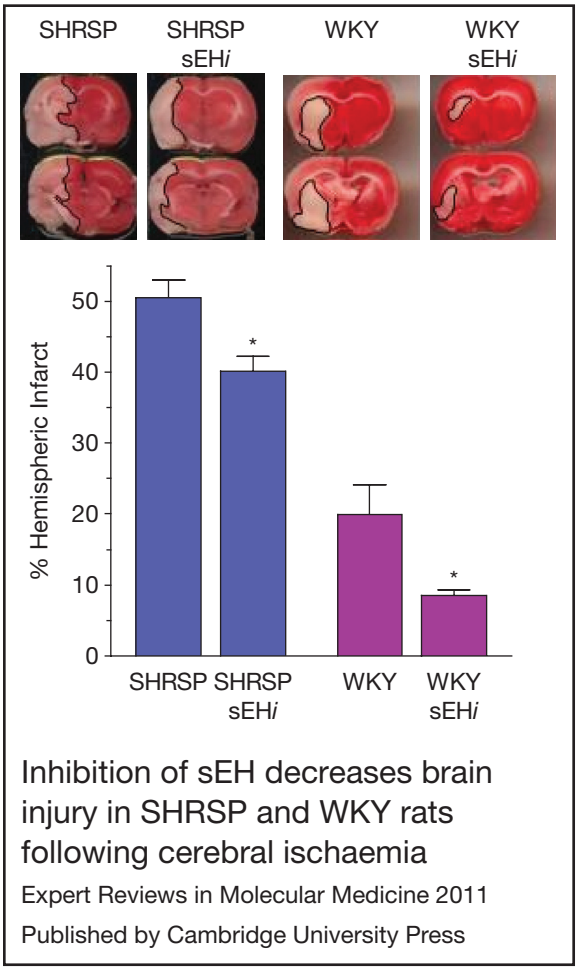

Figure 3. Inhibition of sEH decreases brain injury in SHRSP and WKY rats following cerebral ischaemia. (Top panels) Inhibition of sEH (sEH*i*) decreases infarct size after middle cerebral artery occlusion in SHRSP rats (left) and WKY rats (right), as demonstrated by the representative coronal slices stained with triphenyltetrazolium chloride. (Bottom panel) Quantification of hemispheric infarct size (percentage) in SHRSP and WKY rat groups treated with vehicle and with sEH*i*. Figure adapted, with permission, from Ref. 40 [© 2009, American Society for Investigative Pathology. Published by Elsevier Inc. (2009)]. Abbreviations: sEH, soluble epoxide hydrolase; SHRSP, spontaneously hypertensive stroke-prone; WKY, Wistar–Kyoto.

injury. Inhibitors of sEH have also been administered within hours prior to cerebral ischaemic insult and at the time of reperfusion (Ref. 42). Decreased cerebral injury was found irrespective of the timing of treatment with the sEH inhibitor and appears to be mediated by EETs because CYP epoxygenase inhibition negates the decrease in injury with sEH inhibitor treatment (Refs 41, 42). These experimental studies have provided strong evidence for the fact that inhibiting sEH as a means to increase EET levels protects the brain from injury that occurs with cerebral ischaemic stroke.

Molecular mechanisms of EET action

Interestingly, the mechanisms by which sEH inhibition imparts protection from cerebral ischaemic insult appear to be multifactorial. Experimental evidence supports the notion that cerebral protection by sEH inhibition involves changes in vascular structure and neuronal cell signalling pathways (Refs 39, 40, 41, 42). These changes in the vasculature and neurons appear to alter cerebral blood flow and neuronal cell apoptosis in response to a cerebral ischaemic stroke.

Neuronal protective actions attributed to EETs include reducing astrocytic cell death following oxygen–glucose deprivation (Refs 15, 44, 45). Overexpression of sEH, and human polymorphisms associated with variations in sEH activity, increased cell death induced by oxygen–glucose deprivation (Ref. 34). Hypoxic preconditioning has been found to increase CYP2C11 expression in astrocytes by hypoxia-inducible factor 1α, which provides cytoprotection (Ref. 45). Chronic administration of sEH inhibitor to SHRSP or WKY rat strains resulted in upregulation of antiapoptotic mediators and neuroprotectants in WKY rats and decreased expression of proapoptotic mediators in SHRSP rats (Ref. 40). These findings are in agreement with studies where EETs, CYP epoxygenase overexpression and sEH inhibition have been demonstrated to have antiapoptotic properties (Refs 28, 29).

EETs can inhibit apoptosis by mechanisms that involve *Bcl2* upregulation, inhibition of ceramide production and inhibition of reactive oxygen species (Refs 29, 46). In addition, sEH inhibition was also shown to reduce cell death following hypoxic reperfusion, possibly by antagonising reactive oxygen species (Ref. 47). Chronic administration of sEH inhibitors dampens the enhanced expression of *Fas* and *Tnf* ligands, *Tnf* receptors and *Sphk2* in SHRSP rats, while increasing the expression of several antiapoptotic members of the *Bcl2* gene family, genes encoding

Accession information: doi:10.1017/S1462399411001773; Vol. 13; e7; March 2011

inhibitors of FAS-induced apoptosis (*Cflar* and *Faim*), and the antioxidant-encoding gene *Prdx2* in WKY rats (Ref. 40). In particular, *Mapk8ip* [encoding c-Jun N-terminal kinase-interacting protein (JIP)] was upregulated by AUDA treatment in WKY and SHRSP rats (Ref. 40). JIP has been shown by several investigators to promote tolerance to ischaemia and cellular stress in neuronal cells, and its effects have been attributed to its ability to sequester mitogen-activated protein kinases (MAPKs) in the cytoplasm, preventing gene transcription and thus apoptosis (Refs 48, 49, 50). Increased *Mapk8ip* mRNA expression in the brain has been associated with increased tolerance to cerebral hypoxia in rats (Ref. 51). Lastly, activation of the MAPK and phosphoinositide-3-kinase–AKT signalling pathways could be contributing to not only neuronal but also endothelial cell cytoprotection (Refs 15, 40, 46). Thus, EETs and sEH inhibition have the ability to target several cell types that contribute to protection against cell death following a cerebral ischaemic event.

Protective role for 20-HETE inhibition?

20-HETE also represents a potential therapeutic target for cerebral ischaemia and stroke. There is evidence that *CYP4A11* and *CYP4F2* genetic variants are associated with cerebral infarction in the Asian population (Refs 52, 53, 54). Inhibition of 20-HETE synthesis by using TS-011 protects rats from haemorrhagic or ischaemic stroke (Refs 55, 56, 57). TS-011 was demonstrated to inhibit human recombinant CYP4A11, CYP4F2, CYP4F3 and CYP4F3B hydroxylase enzymes and had no effect on epoxygenase activity (Ref. 55). Inhibition of 20-HETE synthesis eliminated the decrease in cerebral blood flow and cerebral vasospasm after subarachnoid haemorrhage (Ref. 55). In support of a contribution of 20-HETE to cerebral ischaemic stroke, it has been demonstrated that brain 20-HETE levels are increased within 8 h after middle cerebral artery occlusion (Ref. 58). TS-011 significantly improved long-term neurological and functional outcomes following cerebral ischaemia and was associated with reduced brain 20-HETE levels (Refs 55, 56). Another inhibitor of 20-HETE synthesis, HET0016, has also been demonstrated to decrease cerebral damage following cerebral ischaemia (Refs 12, 56, 59). HET0016 decreased brain 20-HETE levels and attenuated the decrease in cerebral blood flow (Ref. 12). A contribution for cerebral-vascular-generated 20-HETE to blood flow and damage following middle cerebral artery occlusion has been demonstrated in SHRSP rats (Ref. 12). SHRSP rats showed a large and sustained postischaemic hyperperfusion compared with WKY rats (Ref. 12). HET0016 eliminated the hyperaemic response in SHRSP rats and was associated with a decrease in cerebral vascular oxidative stress and improved endothelium-dependent dilation (Ref. 12). These findings suggest that higher cerebral vascular 20-HETE levels contribute to oxidative stress and endothelial dysfunction and increase the susceptibility to cerebral damage following ischaemia. The 20-HETE antagonist 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid also reduces infarct size in rats with cerebral ischaemia (Ref. 56). Similar to sEH inhibition, there is evidence that 20-HETE inhibition might decrease ischaemic action through protective effects on neurons in addition to cerebral vascular actions (Ref. 56). More recently, TS-011 was reported to improve defects in cerebral microcirculatory autoregulation near the infarct site, which reduces cerebral ischaemic damage (Ref. 57). Taken together, these studies support the notion that 20-HETE inhibition protects the brain from damage following subarachnoid haemorrhage or cerebral ischaemia.

Cerebral vascular remodelling and CYP eicosanoids

Vascular remodelling is a physiological process that can be triggered by changes in haemodynamics, pressure and other factors and culminates in the reorganisation of the vessel around a larger or smaller lumen. Vascular remodelling occurs with hypertension, arterial stenosis/atherosclerosis and vascular injury (Refs 60, 61). In these disease states, outward remodelling occurs in the vasculature in response to reductions in lumen diameter to maintain lumen diameter in the face of encroachment (Refs 62, 63). In humans this process is successful at maintaining lumen diameter until the stenosis becomes greater than 40% (Refs 62, 63). After this point, the vasculature is no longer able to compensate for the lumen encroachment, and blood flow to end organs becomes compromised.

In hypertension, the large vessels, such as the middle cerebral artery of SHRSP rats, show

Accession information: doi:10.1017/S1462399411001773; Vol. 13; e7; March 2011

hypertrophic outward remodelling that includes increases in blood vessel wall thickness (Refs 63, 64, 65, 66). In addition, chronic hypertension leads to hyperplasia of vascular smooth muscle cells and neointimal formation (Ref. 63). Neointimal formation occurs when vascular smooth muscle cells change phenotypes to the proliferative/synthetic phenotype and invade and proliferate in the media (Refs 60, 61, 62, 67). Vascular smooth muscle cell hyperplasia also occurs with arterial stenosis, atherosclerotic plaque progression and vascular injury (Refs 63, 67). Because all the previously mentioned causes of vascular remodelling increase the risk for, and are pathologically associated with causes for, ischaemic stroke, it is important to elucidate key mediators of vascular remodelling to develop new targets for therapeutics.

EETs

Interestingly, genetic polymorphisms in the sEH enzyme in humans have been linked to the incidence of cardiovascular disease. This association could be related to modifications in sEH activity, and thus EET catabolism (Refs 33, 68, 69). In the Caucasian subpopulation of the Atherosclerosis Risk in Communities (ARIC) study, the *EPHX2* K55R polymorphism results in an increase in the risk for incidence of symptomatic coronary artery disease – that is, myocardial infarction, death or requirement of an intravascular procedure (Ref. 70). Additionally, in the African American subpopulation of the Coronary Artery Risk Development in young Adults (CARDIA) study, having one allele that results in the *EPHX2* R287Q substitution increased the risk for the presence of coronary calcification (Ref. 71). These findings indicate that reduction in sEH activity could result in plaque stabilisation and decreased incidence of acute cardiovascular events resulting from atherosclerosis.

Several experimental studies indicate that sEH inhibition has the potential for protecting against pathological vascular remodelling. Exogenous EETs and sEH inhibition decrease platelet-derived growth factor (PDGF)-stimulated proliferation of vascular smooth muscle cells in cell culture by downregulation of cyclin D1 (Refs 72, 73, 74). CYP epoxygenase overexpression also decreases vascular smooth muscle cell migration stimulated by PDGF through the cAMP/protein kinase A pathway (Ref. 75). Indeed, sEH inhibition decreases collagen deposition in the kidneys of angiotensin-infused hypertensive rats and decreases renal vascular remodelling (Ref. 76). These findings provided the impetus for examining sEH inhibition on vascular remodelling in the SHRSP rat.

The SHRSP rat is an appropriate experimental model of stroke, and SHRSP rats have poor formation of cerebral collateral vessels and reduced microvessel density (Refs 77, 78, 79, 80). One mechanism by which chronic AUDA treatment of SHRSP rats decreased cerebral ischaemic damage was attenuation of vascular hypertrophic remodelling and collagen deposition that occurs in the middle cerebral artery (Ref. 40). Several reports suggest that EETs and sEH inhibition attenuate vascular remodelling by modulating intracellular signalling pathways in vascular smooth muscle cells and fibroblasts (Refs 73, 74). In addition to its effects on the middle cerebral artery, sEH inhibitor treatment increased cerebral microvessel density in SHRSP rats (Ref. 40). This finding is in agreement with reports that EETs induce angiogenesis in several in vivo models and on co-culture of astrocytes and endothelial cells (Refs 46, 81). Because hypoxia and increased metabolic demand are potential triggers for astrocyte EET-mediated angiogenesis, it can be speculated that sEH inhibition resulted in increased cerebral microvessel density by countering the deficiencies present in SHRSP rats (Refs 81, 82). Administration of an sEH inhibitor also improved inward remodelling induced by carotid artery ligation in SHRSP rats to a level that was comparable to that in WKY rats (Ref. 83). Taken together, these results suggest that the cerebral protective effects of sEH inhibition in SHRSP rats were in part due to structural changes in the vasculature.

20-HETE

20-HETE also has the ability to impact cerebral vascular remodelling and microvessel density. PDGF-stimulated migration of vascular smooth muscle cells increases in response to 20-HETE and decreases in the presence of the 20-HETE inhibitor HET0016 (Ref. 84). 20-HETE increases vascular smooth muscle cell migration through MAPK and tyrosine kinase cell signalling pathways (Ref. 84). Correspondingly,

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endothelin-1-induced vascular smooth muscle cell proliferation appears to be mediated by 20-HETE (Ref. 85). However, 20-HETE decreased the proliferation of vascular smooth muscle cells and attenuated PDGF-induced expression of cyclin D1 (Ref. 86). In these studies, 20-HETE increased vascular smooth muscle cell transforming growth factor β levels to mediate the growth-inhibitory effect (Ref. 86). 20-HETE also acts as a nonhypoxic regulator of hypoxia-inducible factor 1α in human microvascular endothelial cells (Ref. 87). Endothelial cell proliferation can be increased by 20-HETE, in part due to activation of vascular endothelial growth factor (Refs 87, 88). These findings support the notion that 20-HETE could impact cerebral vascular remodelling and microvessel density; however, this has not been explored.

Conclusion: expert opinion

The CYP eicosanoid molecular and enzymatic pathway and its contribution to cerebral vascular function provide several opportunities for experimental investigation and therapeutic targeting. In particular, CYP hydroxylase and sEH enzymes and the regulation of cerebral vascular 20-HETE and EETs could influence cerebral blood flow regulation. The complexity of cerebral blood flow regulation has made it difficult to investigate experimentally. Cerebral blood flow autoregulation and neurovascular coupling involve several cell types and expression of different molecular signalling pathways to provide intricate coordination of blood flow (Refs 1, 2, 3, 4, 5, 6). The regulation of CYP eicosanoid enzymes and the generation of 20-HETE and EETs in astrocytes and cerebral endothelial and vascular smooth muscle cells contribute to cerebral blood flow autoregulation and neurovascular coupling (Refs 5, 6, 7). Our understanding of the interaction between cerebral blood flow autoregulation and neurovascular coupling is in its infancy. Experimental studies will require investigation in animal models where there is an absence of cerebral blood flow autoregulation or neurovascular coupling and selective manipulation of CYP eicosanoids in astrocytes, endothelial or vascular smooth muscle cells.

Human genetic studies support the notion that CYP eicosanoids are associated with cerebral vascular disorders. The importance of 20-HETE and EETs has been corroborated by experimental studies in animal models of stroke and vascular remodelling. There have been promising studies in cerebral ischaemia and subarachnoid haemorrhage animal models that demonstrate decreased damage following 20-HETE or sEH inhibition. These would indicate that decreasing 20-HETE or increasing EETs would benefit humans. Experimental findings have also determined that manipulation of CYP eicosanoids improves cerebral blood flow regulation, can positively influence vascular structure and microvessel number, and protects neurons from cell death. Thus, therapeutic targeting of CYP eicosanoids for treating cerebral vascular disorders and stroke demonstrates great promise.

There are several factors and hurdles that will have to be overcome for inhibition of 20-HETE or sEH to result in treatment for humans. One positive for 20-HETE and sEH inhibitors is that researchers and pharmaceutical companies have developed compounds that have been tested in a preclinical setting and an sEH inhibitor actually made it through to human clinical trials (Refs 32, 58). Another aspect for targeting CYP eicosanoids is that these metabolites affect different cerebral cell types and several mechanisms responsible for cerebral vascular disorders. 20-HETE and EETs regulate cerebral blood flow, vascular remodelling, platelet aggregation, angiogenesis and inflammation (Refs 14, 29, 32). In addition, CYP eicosanoids have antiapoptotic and antioxidant actions on astrocytes and neurons. However, even with this great promise for targeting CYP eicosanoids, there are areas of concern. A major concern is that treatments for a stroke after the ischaemic event have in large part been unsuccessful. To date, the ability of manipulating CYP eicosanoids after the ischaemic event to decrease cerebral damage has not been thoroughly investigated. 20-HETE and EET interactions with other eicosanoid pathways or other yet to be defined unwanted actions could limit targeting this pathway for cerebral vascular diseases. The angiogenic action of EETs is one such action that has the potential to accelerate tumour growth in patients with some types of cancer. Alternatively, 20-HETE and sEH inhibitors have the potential to be used as a preventive therapy in patients with cardiovascular diseases who are at higher risks for ischaemic strokes. These preventive therapies

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have a much more difficult path for approval in humans. Therefore, the therapeutic targeting of the CYP eicosanoid molecular and enzymatic pathways for the treatment of cerebral vascular disorders and stroke awaits further investigation.

The importance and contribution of CYP eicosanoids to other neural functions and disorders is beginning to emerge. EETs have been demonstrated to have antipyretic effects in mice (Ref. 89). CYP epoxygenase induction or central EET administration attenuated the fever response to lipopolysaccharide (Ref. 89). Recent evidence provides significant support that EETs can decrease pain through manipulation of neural pain pathways (Refs 90, 91). 14,15-EET activates brain opioid receptors in the ventrolateral periaqueductal grey area to produce antinociception (Ref. 90). Additionally, sEH inhibition reduces inflammation-induced pain and demonstrates promise as an analgesic (Ref. 91). The contribution of CYP eicosanoids to other neurological disorders such as Alzheimer disease or multiple sclerosis has yet to be explored. All in all, there are several unexplored research areas with regard to CYP eicosanoids, cerebral vascular function, and cardiovascular and neurological diseases.

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Further reading, resources and contacts

Iliff, J.J. et al. (2010) Epoxyeicosanoid signaling in CNS function and disease. Prostaglandins and Other Lipid Mediators 91, 68-84
This is an up-to-date review article that focuses on CYP epoxygenase metabolites in brain function.

Imig, J.D. and Hammock, B.D. (2009) Soluble epoxide hydrolase as a therapeutic target for cardiovascular diseases. Nature Reviews Drug Discovery 8, 794-805
This review article highlights the development of inhibitors of soluble epoxide hydrolase that led to human clinical trials for the treatment of diabetes and hypertension.

Marumo, T. et al. (2010) The inhibitor of 20-HETE synthesis, TS-011, improves cerebral microcirculatory autoregulation impaired by middle cerebral artery occlusion in mice. British Journal of Pharmacology 161, 1391-1402
This recent paper describes blood flow autoregulation following cerebral ischaemia in mice administered the Taisho Pharmaceutical CYP hydroxylase inhibitor TS-011.

Simpkins, A.N. et al. (2010) Soluble epoxide hydrolase inhibition modulates vascular remodeling. American Journal of Physiology – Heart and Circulatory Physiology 298, H795-H806
This recent paper presents in-depth experimental evidence on the contribution of soluble epoxide hydrolase to vascular remodelling in SHRSP and WKY rats as well as wild-type and *Ephx2*-deficient mice.

Features associated with this article

Figures
Figure 1. CYP metabolism of arachidonic acid.
Figure 2. CYP eicosanoids in neurovascular coupling and cerebral blood flow autoregulation.
Figure 3. Inhibition of sEH decreases brain injury in SHRSP and WKY rats following cerebral ischaemia.

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