Austin Journal of Anesthesia and Analgesia

Austin Publishing Group

Open Access Full Text Article

Review Article

The Role of GSK in Ischaemic Organ Injury

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Received: August 30, 2014; **Accepted:** September 27, 2014; **Published:** September 30, 2014

Abstract

Glycogen synthase kinase (GSK) 3 is a serine/threonine kinase involved in many signaling pathways with phosphorylation determining its activity. Phosphorylation of the tyrosine 216 residue in the kinase domain causes activation of GSK3 while phosphorylation of the amino terminal serine residue results in GSK inactivation. Hence the dual role of GSK in apoptosis is well documented. The dysregulation of GSK has been linked to many illnesses: cancer, diabetes as well as ischaemic organ injury to name a few. Ischaemic organ injury occurs when there is not enough oxygen to meet the metabolic demands of the tissue and the involvement of GSK in brain, heart, kidney, gut and lung ischaemic organ injury is discussed further here. While GSK is a pivotal multiswitch enzyme, it is becoming an ever increasingly interesting therapeutic target with several drugs undergoing clinical trials.

Keywords: Glycogen synthase kinase; Organ injury; Molecular mechanism; Cellular signaling

Introduction

The diseases associated with depriving organs of their blood supply such as myocardial infarction, stroke or perinatal hypoxic ischaemic encephalopathy are a main cause of death in Europe [1]. Tissue ischaemia can be caused in surgical procedures such as organ transplantation and it is of major concern [2].

When cells are deprived of oxygen, irreversible damage can occur. However, reperfusing the organ, which is restoring blood flow after a period of ischaemia, also induces damage, namely repefusion injury [2], with reperfusion injury causing greater damage than simply the ischaemia alone [3]. This can lead to MODS (multiple organ dysfunction syndrome), which is fatal. Hence it is important to understand the pathophysiology behind ischaemia and ischaemia reperfusion injuries. Ischaemia is described as "inadequate oxygen delivery to cover the metabolic demands" of the tissue [2]. Ischaemia is regarded as a proinflammatory state as there is an increase in inflammatory molecules such as cytokines with a reduction in the more protective molecules [4].

There are molecular changes that occur when a tissue goes through ischaemia. Adenosintriphosaphate (ATP) is not resynthesized, but there is an increased breakdown to ADP and AMP and hypoxanthine. This change in ATP levels initiates the apoptotic cascade that results in cell death [5]. Hypoxanthine, in normal physiological settings, is oxidized by xanthine dehydrogenase to xanthine. However, in this hypoxic setting, the hypoxanthine is converted to xanthine oxidase, the O form. This form of xanthine oxidase has been shown to produce reactive oxygen species when oxygen is present again (reperfusion) [6]. These reactive oxygen species damage the tissue through lipid peroxidation [7].

The reperfusion injury that follows ischaemia increases the damage already created by ischaemia [8]. It doesnot just encompass local damage with reactive oxygen species, but also leads to systemic changes [2] and can increase the damage already created by ischaemia. It is characterised by tissue oedema and increased vasculature permeability to protein [3].

The endothelial cells that line blood vessels are particularly sensitive to changes in oxygen levels and hypoxia triggers processes that lead toendothelial dysfunction.Neutrophils adhering to the surface of the endothelium cells are an essential step [3] with adherence to the vessel importance for vessel injuries. They release enzymes such as elastase [3] and block the capillaries, resulting in "the no-flow phenomenon", which further increases the effect of the hypoxia. The no flow phenomenon describes the reduced flow of blood to an organ following ischaemia.

It also decreases the production of positive agents such as nitric oxide, prostacyclinand vasodilators whilst increasing the production of others, such as endothelin1 [1], a powerful vasoconstrictor. Endothelial swelling follows these processes with reduced capillary perfusion [9]. As ischaemia and reperfusion injuries are of significance, it is imperative to understand enzymes that play a role in such injuries in multiple organs; GSK3 is one of these enzymes.

Molecular structure of GSK

The enzyme, Glycogen Synthase Kinase (GSK) is a proline directed serine/threonine kinase involved in many signaling pathways in mammals [10]. There are 2 isoforms of GSK: GSK3α andGSK3β, with molecular weights of 51kdaand 47kda respectively [11]. The structure of these kinases is an N terminal lobe made up of β sheets and a C terminal lobe consisting of α helices [12] with the ATP region between both these lobes. They are highly homologous [10] with the two isoforms having a sequence identity of 95% in the catalytic domain and a serine residue, which are inhibitory residues [13] near the N terminus [14]. It is the phosphorylation of the N terminus that determines the GSK enzymatic activity [15] with ser21 present for GSK3α and Ser9 for GSK3β [16]. In the case of GSK3β, ser9 acts as an inhibitor by blocking the binding of substrates to the catalytic site [13].

The activating residues ofGSK3α andGSK3βare tyrosine 279

Citation: Mitchell S, Guo J, Zhou H and Ma D. The Role of GSK in Ischaemic Organ Injury. Austin J Anesthesia and Analgesia. 2014;2(7): 1037.

and tyrosine 216 respectively [13]. When Tyrosine 216 is not phosphorylated, it prevents substrates from entering the catalytic site but phosphorylation of tyr216 stops this [13]. When Tyrosine 216 is phosphorylated it allows substrates to enter the catalytic site activating GSK3β. It has however been noted that the difference between the two is due to the glycine [17] rich extension at the N terminus of GSK3α, with the N terminal end in GSK3α 63 residues longer than the β isoform [18]. In addition to this, a variant of GSK3β has been identified: GSK32.

GSK belongs to the mitogen activated protein kinase family members [17] with the sequence of GSK3β 41% similar to the sequence of cyclin dependent kinase 2 (CDK2) [18,19]. However, the substrates of GSK need a Carboxyl- terminal priming phosphate at (n+4) to be phosphorylated [19]. Nis the site of phosphorylation demonstrating its substrate specificity. This primed phosphorylation has a 100-1000 times greater efficiency than phosphorylation that does not involve priming [18] although it is not strictly necessary [14].

Only recently has the binding site for the priming substrate on GSK3β been located and it includes 3 amino acid residues: arginine 96, Arginine 180 and lysine 205. There is also a large presence of GSK3β in the brain [20], which has a particular importance for ischaemic and reperfusion injuries.

Function of GSK

Initially, over 20 years ago in 1980,GSK was thought to only be used in the phosphorylation of glycogen synthase, inhibiting the final step of glycogen synthesis [17]. However, since then, the physiological function of GSK3 has been discovered from genetic analysis in drosophilia [21,22], dictyostelium [23] and yeast [24,25]. It is now considered a ubiquitous multiswitch enzyme and is known to phosphorylate up to 50 substrates [26] including the transcription factors c- jun, c- myb and c- myc [25]. It also phosphorylatesB catenin and the APC tumour suppressor protein [27] enabling it to modulate metabolism, gene expression [28] and play a pivotal role in oxidative stress induced neuronal apoptosis [29]. With a link to many cellular processes, the dysregulation of GSK is linked to many diseases such as Cancer [30], Alzheimer's disease [31] and Diabetes [14]**.** Even with similar structures, the two GSK isoforms have different functions. GSK3β null mice have an embryonic lethal phenotype [32] as it is essential for the formation of the embryonic axes [33,34].

GSK3β is known to influence the transcription factor, NfKβ and it is believed that this is the reason for its involvement in many of the inflammatory processes [35]. GSK3β is of particular **interest as it** can control blood glucose levels via insulin [18] and therefore it has a role in the development of insulin resistance and type 2 diabetes. Studies have shown that GSK level is elevated in the skeletal muscle of obese patients and patients suffering from type 2 diabetes [36]. Insulin activity causes GSK inhibition via the well-known phosphoinositide 3 kinase (P13-K) signal transduction pathway [15]. P13K activates PKB (Akt), causing phosphorylation of serine 9 and 21 on the respective GSK isoforms. This prevents GSK activity towards substrates such as glycogen synthase and leads to substrates dephosphorylation and activation [17].

Cell fates during embryonic development are another role of GSK and works via the Wnt growth factor signalling pathway [19]. Wnt is essential in cellular proliferation, differentiation, motility and polarity of cells [37]. In the absence of wnt, GSK phosphorylates β catenin, downstream of Wnt and causes its ubiquination and degradation in cells [14]. Although the precise mechanisms by which Wnt inhibits GSK activity towards β catenin remains unclear [15], it has been shown to involve the "destruction complex" consisting of GSK3, Axin/conductin, β catenin and adenomatous polyposis coli (APC) [38]. This again alludes to the importance of GSK in cancer, here through APC, a tumour suppressor gene.

Role of GSK in cell death/organ injury

GSK3β has been shown to have opposing actions on apoptosis [28] induced cell death. This discovery was made when hepatocyte apoptosis occurred in GSK3β knockout mice during embryonic development [32] opposing previous discoveries where expression of GSK3β caused apoptosis. This ability is due to GSK3β promoting the intrinsic apoptotic signaling pathway and inhibiting the extrinsic apoptotic pathway [39]. Activation of GSK3β is caused by phosphorylation of the tyrosine 216 residue in the kinase domain and inactivation is caused by phosphorylation of the amino terminal serine residue [29].

The Bcl-2 family comprises of both pro apoptotic and anti-apoptotic proteins such as bax and bid respectively [40]. The ratio of pro apoptotic to anti apoptotic Bcl-2 family members determines whether the intrinsic pathway is activated [41]. Many stimuli can activate the apoptotic pathway such as DNA damage, stress and hypoxic ischaemia [39]. The pro-apoptotic proteins undergo conformational changes as it migrates from the cytoplasm to the mitochondria [39]. This sequesters the opening of the Mitochondrial Permeability Transition Pore (MPTP) with loss of mitochondrial membrane potential and release of cytochrome C, a component of the electron transport chain [42] from the mitochondria to the cytosol [43]. Cytochrome C forms the apoptosome, which activates caspase 9, an initiator caspase and then subsequently activates caspase 3, the most important executioner caspase [42], resulting in the degradation of chromosomal DNA, ultimately leading to cell death.

The extrinsic pathway, involves death receptors of the tumour necrosis factor family, which all share a similar extracellular domain, the death domain. This then involves the formation of the death inducing signaling complex (DISC) [44], which contains Fas, a member of the tumour necrosis factor family. Disc then activates caspase 8, which activates caspase 3 and results in cell death [45]. As GSK3 plays an important role in apoptosis, it is important to analyse the role that GSK plays in ischaemic organ injury

Brain: GSK3β localization has occurred in some areas of the human brain [46] and is present in the central nervous system [47]. The brain is dependent on continuous blood supply and interestingly, the ATP level in the brain completely diminishes within 4 minutes [48]. Stroke, a result of brain ischaemia, is a common occurrence.

There have been numerous studies demonstrating the involvement of GSKβ in brain ischaemic injury. In transient global cerebral ischaemia, induced by bilateral common carotid artery occlusion for 5 minutes with hypotension, phospho – GSK3β, ser 9 and phospho-Akt, ser 473 were increased in the CA1 hippocampal subregion of mice brains suggesting Akt/GSK3β signaling mediates survival of

hippocampal neurons [49]. After hypoxic ischaemia in 7-day-old neonatal rats, levels of IGF-1, pAKT and pGSK3 were measured. It was found that IGF- 1 caused the activation of Akt during recovery after HI and caused inactivation of GSK3βby phosphorylation of serine 9. During reperfusion, there was a redistribution of GSK3β from the cytosol to the nucleus [50].

Traumatic Brain Injury (TBI) is a neurological condition linked with depressive behavior [51] activating pathways that involve apoptotic or anti-apoptotic signaling. TBI caused increased phosphorylation of serine 9 GSK3β, the inhibitory form [51]. With this in mind and prior knowledge of the involvement of GSK3 in apoptotic pathways, it makes GSK3β an ideal therapeutic target.

Heart: Coronary heart disease is a huge worldwide burden, with ischaemic injury a cause of myocardial infarctions [52]. Studies have demonstrated that GSK3β plays a role in cardioprotection with GSK3β involvement in ischaemic preconditioning [53]. Inhibitors of GSK3β added to an in vivo model before ischaemia or at the beginning of reperfusion were shown to decrease necrosis**.** Anaesthetized Sprague Dawley rats underwent 30 minutes of myocardial ischaemia and 6 hours of reperfusion with or without the addition of the GSK3inhibitor TDZD-8. Addition of the inhibitor decreased MI size, neutrophil infiltration, suppressed NF-kB and p38 MAPK [52]. It has been shown that the B adrenergic receptor causes apoptosis in cardiac myocytes *in vitro* and *in vivo* [54,55] with evidence that it increases GSK3 activity. Singh et al demonstrated that extracellular ubiquitin, used for protein turnover, possesses protective properties through the inactivation of GSK3β/JNK and the mitochondrial pathways [54].

As further evidence that GSK3β has an effect on heart ischaemic conditions, the treatment of cardiac H9c2 cells, ratcardiomyoblast cell line, with exogenous zinc chloride prevented cardiac reperfusion by increasing the phosphorylation at serine 9 GSK3β [56]. These studies again demonstrate the pivotal action that inhibition of GSK3βhas, on organ survival following ischaemia.

Kidneys: Acute ischaemic renal failure commonly causes death**.** In transient renal artery occlusion in rats, *in vivo*, GSk3β was demonstrated to be involved in kidney dysfunction after stress or ischaemia through bax activation, apoptosis by disturbing the balance of pro and anti-apoptotic proteins and tubular cell injury [57]. The study demonstrated that GSK3β phosphorylates Bax at the ser163 residue [57]. Renal ischaemia also increases reactive oxygen species, which has been linked to GSK3β activation [58].

Vasileva et al showed that the inhibition of GSK3β is important in the protective cascade after renal ischaemia through precondition with lithium and insulin. Phosphorylation of the serine 9 residue of GSK3β increases Nonspecific Mitochondrial Permeability (NMP) activation, which decreases cell death [59]. Inhibition of GSK was analysed on a mouse model of endotoxaemic acute renal failure to look at cell death, renal dysfunction and TNFα induced cytotoxicity. It was shown to decrease lipopolysaccharide-induced production of TNFα, RANTES and NFkβ [57]**.** As ischaemia is one of the main causes of renal failure and renal failure contributes largely to mortality in the UK, discovering ways to protect the kidney are highly important.

Gut: Gut ischaemia and reperfusion injury are greatly influenced by the transcription factor NFKβ, which is a substrate of GSK3β (Wang et al.). Cuzzocrea et al demonstrated that the GSK3β inhibitor, TDZD-8 weakened apoptosis, NFkβ expression, ICAM expression and neutrophil infiltration amongst other factors when applied to an SAO animal model. This model involves ischaemia and reperfusion to splanchnic organs. It was deduced from these results that inhibiting GSK3β stops the interaction between neutrophils and endothelial cells at the early and late of neutrophil transmigration [60]. GSk3β is also involved in intestinal epithelial cells wound healing response. Phosphorylation of serine 9 residue of GSK3 in IEC18 cell epithelial cell monolayers and inhibition of B catenin nuclear translocation was also found, suggesting the importance of GSK3β in wound healing.

Lungs: GSK3 action is also noted in the lungs. The presence of the GSK3/ β catenin axis plays an important role in airway smooth muscle cell proliferation as well as GSK being involved in lung injury. Cuzzocrea et al, one of the studies showing the involvement with the lungs, demonstrated that mice treated with bleomycin developed significant lung injury. However, with administration of TDZD-8, a GSK3β inhibitor, the lung injury sustained was reduced. With evidence that GSK plays an important role in the physiology of the damage caused to many organs following ischemia, this makes it an attractive therapeutic target.

GSK as therapeutic target

GSK is a multi-tasking kinase [14] involved in the necrotic and apoptotic processes of many tissues with involvement in several pathological conditions, so it has become a common pharmacological target with increasing research to inhibit its actions. Lithium, the first GSK3β inhibitor discovered and sodium valproate, another drug shown to inhibit GSK3, are both important in the treatment of depression and bipolar disorders [61]. Lithium, which is also a commonly used mood stabilizer [62], has been shown to protect neurons against glutamate excitotoxicity [63] and studies have implied that it can be used in the treatment of acute brain injuries. Klein and Melton first discovered that lithium could inhibit GSK3β [64] and this was later supported by a rat brain model [65], by phosphorylation of the serine residues on both the α and β isoforms [62]. Sodium Valproate, another mood stabilizer and anti-convulsant drug, inhibits GSK3 and prevents the HIV-1 damage caused to the nervous system [66].

Alzheimer's is another disorder that is influenced by GSK-3 [30]. Thiadiazolidinones (TDZD), non-ATP competitive inhibitors of GSK-3 can prevent hyperphosphorylation [67]. The neurofibrillary tangles that are characteristic of Alzheimer's pathology are composed of a highly phosphorylated form of the microtubule associated protein, TDZD [68]. Hence, thiadiazolidinones have been implicated in the treatment of Alzheimer's [67,69,70].

Some synthetic GSK inhibitors have been developed, with two inhibitors SB-216763 and SB- 415286 shown to protect against neuronal cell death [71]. However, a reported complication with such inhibitors is the build-up of β- catenin, which is linked to the development of cancers, namely colon and melanomas [72].

Another GSK3 synthetic inhibitor, AR-A014418, was found to reduce the immobility time in rats that underwent a forced swim test, which is used to analyze antidepressant efficacy [65]. As well as being a target in brain disorders, inhibition of GSK maintains

the pluripotency of embryonic stem cells [73]. 6-bromoindirubin-3-oxime (BIO), the specific inhibitor of GSK3β, activates the wnt signaling pathway, and maintains the undifferentiated phenotypes of the ESC as well as increasing the specific transcription factors such as Oct3/4 and Nanog to maintain pluripotency [73].

Along with the inhibitors ability to affect neuronal cell death, SB-216763, SB- 415286 and TDZD-8 were also able to decrease nuclear factor kappa B p65 activity and therefore decrease inflammation in organs [74]. GSK3b is also involved in the pathophysiology of diabetes and therefore its inhibition could help disease progression with the discovery of many GSK3b inhibitors for this purpose.CT20026 was shown to improve oral glucose tolerance in diabetic obese rhesus monkeys with longer treatment decreasing diabetic progression [75]. 3-aminopyrazole, the water-soluble inhibitor of GSK, administered to 18 hour fasted ob/ob mice was also shown to significantly lower blood glucose levels [74]. Pyrrole-2,5-diones has also been administered to ZDF rats and its ability as an oral active GSK3b demonstrated [76]. Although the majority of the studies have been conducted in rats, these are promising results. With ischaemic and reperfusion injuries a major worry in healthcare, such advances are ever more important.

Conclusion

GSK-3 has been shown to be hugely important in many signaling pathways and it is relevant in a multitude of disease pathophysiology. Ischaemia causes a great deal of damage to organs with the involvement of GSK in this process. The phosphorylation and inhibition of GSK prevents the opening of the mitochondrial permeability transition pore (mPTP) and is known to be protective in ischaemic reperfusion injuries [77]. With these properties, it has become an interesting therapeutic target with the use of many GSK3 inhibitors currently being trialed [78]. These trials are still in the early stages, but nevertheless are an important development in scientific research.

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Austin J Anesthesia and Analgesia - Volume 2 Issue 7 - 2014
ISSN : 2381-893X | www.austinpublishinggroup.org

Citation: Mitchell S, Guo J, Zhou H and Ma D. The Role of GSK in Ischaemic Organ Injury. Austin J Anesthesia and Analgesia. 2014;2(7): 1037.