*Perspective*

# The Role of Galectin-3 in Stroke and Diseases of the Cerebrovascular System

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## ABSTRACT

The carbohydrate binding molecule Galectin-3 has been the focus of recent study in a variety of disease processes, and there is evidence that it plays a role in diseases of the cerebrovascular system. In this review, we summarize the relevant clinical literature on the role of Galectin-3 in ischemic stroke, intracranial hemorrhage and subarachnoid hemorrhage. We also provide a brief overview of the cellular and molecular mechanisms behind the role played by Galectin-3 following ischemic brain injury. Our review is aimed at clinicians who manage these conditions, and neuroscientists who study the role of biomarkers in cerebrovascular disease.

**Keywords:** Galectin-3; stroke; intracranial hemorrhage; subarachnoid hemorrhage; cerebrovascular; biomarker


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## 1 INTRODUCTION

Although most of the attention in the research literature on the carbohydrate-binding lectin Galectin-3 has focused on cardiovascular pathology [1], especially in heart failure [2], there have been some recent studies discussing its role in cerebrovascular disease [3,4]. However, the results of these studies have not been completely consistent with each other [5–8], and awareness in the neurosciences community about this biomarker remains limited.

In this review, we summarize the literature on Galectin-3 in relation to diseases of the cerebrovascular system.

## 2 BIOCHEMISTRY AND PHYSIOLOGICAL ROLE OF GALECTIN-3

Galectin-3 is also known as Mac-2 or Carbohydrate Binding Protein-35 (CBP-35), and is encoded by the LGALS3 gene on Chromosome 14 [9]. It influences cell function through binding to Galactoside sugars, part of the intercellular carbohydrate-based signaling known as "glycocodes" [10–12].

Galectin-3 is widely distributed throughout the body, in various cells as well as in the extracellular space [11]. In the brain, ependymal cells and astrocytes of the subventricular zone express Galectin-3, and expression is increased following brain insults, especially from the microglia [7,13–15].

## 3 GALECTIN-3 IN STROKE AND CEREBROVASCULAR DISEASE

### 3.1 Pathophysiology of Galectin-3 in brain ischemia

Galectin-3 levels are most elevated in the 60–96 hours post focal brain ischemia in animals [16,17] though some expression persists even after 2 months [14]. The primary source of Galectin-3 in the acute ischemic brain tissue is the microglia. Studies in a mouse model of transient brain ischemia found that the area of the infarct and the apoptotic neuron count were increased when Galectin-3 positive microglia were ablated. Similar findings were seen in mice which were genetically deficient in Galectin-3 [18,19]. At the same time, it is seen that Galectin-3 is associated with an early inflammatory response in ischemic brain tissue. The cytokine-like activity of Galectin-3 is suggestive of it being part of an endogenous danger signaling pathway for the central nervous system [20] Galectin-3 expression leads to infiltration of inflammatory cells, and then the production of reactive oxygen species [21].

After the hyperacute phase, the pro-angiogenic effects of Galectin-3 help in revascularization of previously ischemic tissue. When Galectin-3 was blocked, post stroke angiogenesis was decreased in rats [14]. In the longer term, Galectin-3 is likely to play an important role in remyelination and recovery from neuronal loss. In vitro, it is known to promote neurite outgrowth and cell adhesion [22]. An upregulation of Galectin-3 levels is also noted in oligodendroglia when differentiating, and remyelination is impaired in mice who have genetic deficiency of Galectin-3 [23,24]. It is possible that myelin phagocytosis by microglia is upregulated in a pathway that involves Galectin-3, and since it is known that the presence of myelin can inhibit the differentiation of oligodendrocytes [25], this might be the mechanism behind the association with remyelination.

It is likely that the pluripotent role of Galectin-3 is responsible for the heterogeneity of results seen in knockout and inhibitor studies, because initial inflammatory effects and later reparative, pro-angiogenic and fibrotic effects may lead to opposing effects on lesion size and long term outcome.

Interestingly, one small study of patients with Cerebral Autosomal Dominant Arteriopathy with subcortical infarcts and Leukoencephalopathy (CADASIL) found that anti-Galectin-3 antibodies bound more the cerebral walls of CADASIL patients than to those of controls [26]. This suggested a change in the characteristics of the blood vessel lining in these patients.

### 3.2 Clinical evidence

#### 3.2.1 Ischemic stroke

A recent study based on the REGARDS cohort of blacks and whites found that Galectin-3 levels were associated with ischemic stroke incidence in individuals who were younger than 64 years of age [3]. The reason for such an association with age is not clear, but it is possible that levels correlate with a generalized worsening of metabolic syndrome markers, which are more likely to pass the diagnostic threshold later in life. However, this relationship has not been consistently noted in all studies. A study from a Finnish cohort [27] only found a weak relationship with stroke incidence over 15 years of followup, with attenuation following multivariable adjustment.

Apart from incidence in the general population, there have been a few investigations into whether Galectin-3 levels influence the risk of ischemic stroke in specific high risk populations. Once again, consistent results have not been reported. A 2016 study found that patients with higher Galectin-3 levels in the blood were more likely to suffer ischemic stroke after carotid endarterectomy, even after correcting for other risk factors [28]. Serum levels of Galectin-3 rise along with the rise of the atherosclerotic burden in the body [21], and a similar relationship is found specifically for carotid atherosclerosis [21,28]. On the tissue level, it has been found that Galectin-3 levels are upregulated in particularly unstable regions of the carotid plaques [29]. A somewhat contradictory finding came from Kadoglou *et al.*, who found that intra-plaque Galectin-3 levels were lower in symptomatic patients with carotid atherosclerosis, than those who were asymptomatic [6]. Of note, higher intra-plaque Galectin-3 levels were associated with echogenicity of the plaques, and symptomatic patients had

less echogenic plaques, which might have been a confounding factor. We suspect that the role of Galectin-3 in these plaques varies over time—initially, the role is pro-inflammatory, and as plaques get established, its role in the fibrotic pathway comes into greater prominence.

Similarly, in patients with new onset atrial fibrillation, which is also a major ischemic stroke risk factor, blood levels of Galectin-3 were elevated, and correlated with CHADS2Vasc scores [30]. However, a study of 1013 high-risk patients who underwent coronary angiography following cardiovascular events in Italy found no association between Galectin-3 levels and past history of stroke, or future stroke incidence [31]. A study from China on 284 patients with Diabetes mellitus also found no influence of Galectin-3 levels on the odds of stroke [32].

Larger studies will be needed to settle the relationship between Galectin-3 and incident ischemic stroke. When it comes to prognosis, one small study found that Galectin-3 levels were not predictive of outcomes acutely and at 3 months in stroke patients who received intravenous tissue plasminogen activator [33]. However, patients did have higher Galectin-3 levels than controls, which is consistent with some of the studies that have been discussed earlier.

#### 3.2.2 Intracranial hemorrhage

There is limited data on the role of Galectin-3 in intracranial hemorrhage. Since the mechanisms of injury are different from that seen in focal ischemia, it is not possible to extrapolate from the findings of ischemic stroke studies. In one study [34] that compared 110 patients with acute intracerebral hemorrhage against 110 controls, plasma levels of Galectin-3 were higher in the patients. They also found this to be an independent prognostic predictor for mortality at 1 week and 6 months, as well as for 6 month overall survival and unfavorable outcomes. The predictive ability as indicated by the area under the curve was similar to that for markers of clinical severity and hematoma volume.

#### 3.2.3 Subarachnoid hemorrhage

Two recent studies have assessed the role of Galectin-3 in subarachnoid hemorrhage. In the first study, on 120 Chinese patients with aneurysmal subarachnoid hemorrhages, plasma Galectin-3 levels were higher than in controls, and these levels were independent predictor of poor outcomes and mortality at the 6 month mark [35]. Higher Galectin-3 levels were also correlated with higher grades of subarachnoid hemorrhage—this might be because of higher levels causing or being a marker of a more robust inflammatory response, or perhaps because patients with higher Galectin-3 levels were already predisposed to more severe bleeds, which might arise from subclinical vascular pathology.

## 4 CONCLUSION

Our understanding of the role of Galectin-3 in the diseases of the vasculature of the central nervous system remains limited. Studies are beginning to reveal that the molecule has a variety of functions, which change over the course of time after brain injury. Further investigations, both clinical and tissue-based, will be of great importance in delineating its function further, and in assessing its value as a biomarker of cerebrovascular pathology.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest, and no disclosures.

## AUTHOR CONTRIBUTIONS

A.V. conceptualized the manuscript. A.V., A.K. and N.K. contributed to literature review. A.K. and N.K. were responsible for text and critical revisions. All authors reviewed the final manuscript and are in agreement with its content.

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