European Review for Medical and Pharmacological Sciences 2020; 24: 10054-10060

Association between caveolin-1 and stroke: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Caveolin-1 plays critical roles in regulating signal transduction and cholesterol trafficking in cells. However, the relationship between caveolin-1 and stroke remains less reported.

MATERIALS AND METHODS: In this study, we reviewed information from seventeen studies to get the qualitative evidence of the influence of the caveolin-1 on stroke and collected data from three of the seventeen studies to conduct meta-analysis. The original studies classified participants into two groups with stroke group and control group, respectively. The random-effect model was used in the meta-analysis with the standardized mean difference (SMD) as the measure indicator.

RESULTS: Our data showed that the SMD (95% confidence intervals, CIs) between the control group and the stroke group was -0.5449 [-2.3344, 1.0000]. For the subgroup analysis, The SMD (95% confidence intervals, CIs) between the control group and the ischemic stroke group was -1.4589 [-5.0129, 2.0951], and between the control group and the hemorrhagic stroke group was 0.3438 [-0.4140, 1.1017].

CONCLUSIONS: Although the differences are not statistically significant between the two groups, the high level of caveolin-1 are associated with the stroke, which may remedy the stroke. Besides, an opposite result was observed for the association of the caveolin-1 on the ischemic stroke and hemorrhagic stroke. To confirm this association, further studies are necessary.

Key Words:
Caveolin-1, Stroke, Ischemic stroke, Hemorrhagic stroke.

Introduction

Stroke is the third leading cause of death in industrialized countries resulting in permanent disability in adults worldwide frequently[1]. Stroke contains hemorrhagic stroke (HS) and ischemic stroke (IS) which is the most common form of stroke. While hemorrhagic transformation, particularly severe hemorrhage, is the most feared neurovascular complication of tissue plasminogen activator thrombolysis[2]. Multiple factors can influence the development of stroke, for example, the age, gender, smoking, alcohol intake, hypertension, diabetes mellitus, and genetic factors[3]. Although different mechanisms are involved in the pathogenesis of stroke, increasing studies[4-8] show that ischemic injury, inflammation, and reverse cholesterol transport account for its pathogenic progression.

Currently, most researches aimed at cellular mechanisms of the stroke according to animal trials[9-13]. However, cell death is not a direct cause of patient death in the acute phase. Rather, most patients with a cerebral infarction die of brain edema and hemorrhagic transformation in ischemic brain tissues[14]. Brain edema ultimately causes enlargement of the infarction after stroke[15,16]. Hemorrhagic transformation is a well-recognized complication that limits the use of or negates the effects of thrombolytic treatment and occasionally results in death[17].

Caveolin-1 is a regulatory protein of the arterial wall, which is the main coat protein of caveolae being micro-invaginations of the cell plasma membrane[10]. Caveolin-1 is responsible for regulating various signaling molecules and participates in cellular cholesterol transport and homeostasis[18]. Caveolae and caveolin-1 have been combined as pivotal targets in the control of various important cellular processes such as protein trafficking, lipid metabolism, and signal transduction[19]. Caveolin-1 is expressed ubiquitously,

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which is high expressed in adipocytes, endothelial cells, fibroblasts, and smooth muscle cells[20]. Moreover, increasing evidence suggests an important role for caveolin-1 in the injured brain[21-24]. However, few studies reported the effects of the caveolin-1 on stroke.

In the present study, we attempt to synthesize all the related information coming from previous literature to investigate the association between caveolin-1 and stroke and its underlying mechanisms. Moreover, we also attempt to explore the distinction of the caveolin-1 between hemorrhagic stroke and ischemic stroke.

Materials and Methods

Publication Search

We systematically searched for studies about the association of caveolin-1 with the risk of stroke in the electronic databases PubMed and Web of Science (before 20 September 2018) with detailed search terms for: "caveolin-1" or"CAV1" and "stroke" or "cerebral hemorrhage" or "hemorrhagic stroke" or "ischemic stroke" (see Figure 1 for detailed search strategy). Studies conducted in humans or animal could be included in this article. All the procedures were conducted by two reviewers (Ling Feng and Yutao Fang) independently and any discrepancies were resolved through discussion and consultation with a third reviewer. We reached the objective literature as follows. First, we combined the keywords to search the references from the two electronic databases, and then, removed the duplicated records. After that, according to the title and abstract, we screened those deduplicated records. Lastly, we read the remainder full-text articles in-depth to identify the aim of the articles.

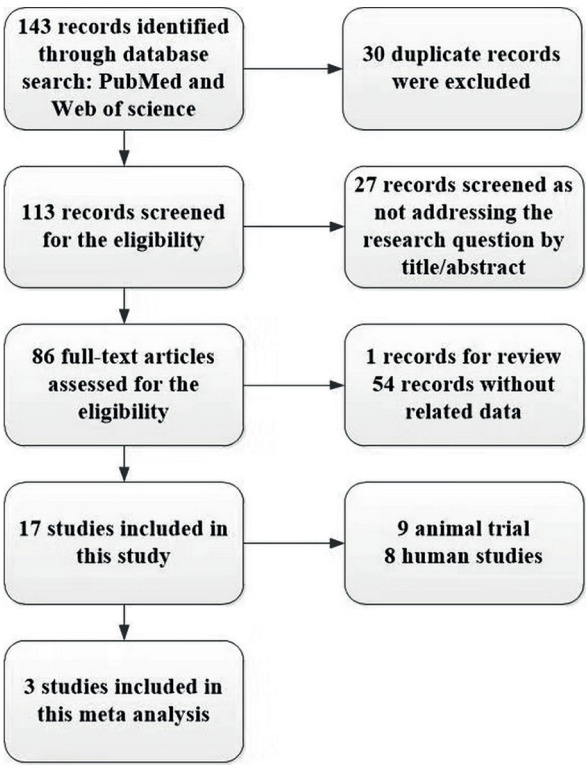

Figure 1. Flow diagram of study selection.

Inclusion and Exclusion Criteria

The quality of each selected study was assessed by 2 reviewers, and disagreement was resolved through discussion and consultation with a third reviewer. We selected studies based on the following criteria. For the systematic review, they must investigate the influence of caveolin-1 on stroke; while for the meta-analysis the original studies were included if (1) the original data was presented with the mean and standard deviation of the caveolin-1; (2) they must be quantitative to investigate the association between the stroke and caveolin-1; (3) the original data could be divided into different exposure groups; (4) the data can be obtained; (5) only randomized control clinical trials were included. In this meta-analysis, we only included publications in English. The articles have been excluded when (1) they were significantly concentrated on molecule level and (2) the paper was a review or report.

Statistical Analysis

All statistical analyses were conducted using R software with "metafor" package (v.3.22 https://cran.r-project.org/). Random-effects models were used to synthesize the association between the caveolin-1 and stroke[25]. Random-effect models gave more weight to smaller studies and had typically wider confidence intervals because in addition to the within-study variance, they also considered potential variation between the true effects that all included studies estimate[26]. SMDs and their corresponding 95% confidence intervals (95% CIs) were used to assess the influence of the caveolin-1 on the stroke. What's more, we conducted two subgroup analysis to assess the influence of the caveolin-1 on the hemorrhagic stroke and ischemic stroke. The p-value less than 0.05 was considered statistical significance. All the p-values were obtained using a two-sided test. We described the between-study heterogeneity

Table I. Major characteristics of the studies included in the meta-analysis.

Study	Year	Location	Period	Sample	Age (SD)	
					Control	Stroke
Bang et al[28]	2016	Korea	2008-2014	129	61.2 (13.7)	55.7 (9.9)
Castellanos et al[29]	2018	Spain	–	133	71.0 (13.0)	75.0 (13.0)
Zhang et al[30]	2016	China	2013-2014	238	63.2 (9.1)	65.0 (8.7)
Zhang et al[30]	2016	China	2013-2014	213	63.2 (9.1)	65.1 (8.4)

by using the I^2 metric and the between studies' variance using tau^2. We assessed publication bias using the Egger's test for asymmetry[27].

Results

Summary of Collected Data

Figure 1 provided a detailed flow diagram of the search process for this systematic review and meta-analysis. We got 143 literature from the electronic databases overall. The remainders of records were 113 from the databases after the de-duplication, and all were assessed for their abstract and title. 86 studies were further assessed for their full texts. Seventy studies experienced in-depth review, with three studies fulfilling the inclusion criteria eventually which were used to conduct meta-analysis.

Study Characteristics

Table I[28-30] showed the details of the studies information. A total of three articles were selected in this meta-analysis fulfilling exclusion and inclusion criteria, which included 226 stroke cases and 487 control cases. One study focused on hemorrhagic stroke[28], one study focused on ischemic stroke[29], and one study focused on hemorrhagic stroke, as well as ischemic stroke[30]. We collected the original data of the caveolin-1 (mean and standard deviation) from the three studies. In addition, all the subjects shared a common age characteristic from 55.7 to 75.0 years (the mean age).

Main Findings for Those Studies

Table II[28-30] provided details of the main findings. Caveolin-l level significantly differed between stroke patients and control. Caveolin-l

Table II. The main findings of these papers.

Study	CAVEOLIN-1 (SD/Range)		Type	Statistical methods	Main findings
	Control	Stroke			
Bang et al[28]	1.313 (0.498)	0.929 (0.535)	IS	ANOVA: Group-differences testing	There were significant differences; There was no correlation between caveolin-1 level and infarct size
Castellanos et al[29]	0.07 (0.0-0.20)	0.24 (0.17-0.40)	HS	*t* or *U* test: Group-differences testing	Serum caveolin-1 levels at admission were significantly higher in patients than in controls
Zhang et al[30]	5.62 (2.63)	5.71 (2.77)	IS	*t* or *U* test: Group-differences testing; logistic regression: evaluate the relationship	There were no significant differences
Zhang et al[30]	5.62 (2.63)	4.74 (2.26)	HS	*t* or *U* test: Group-differences testing; logistic regression: evaluate the relationship	Patients had lower serum caveolin-1 levels

level in ischemic stroke patients was significantly higher than that in hemorrhagic stroke patients, but statistically lower than that in the healthy controls. Bang et al[28] found that Caveolin-1 level did not differ by the time interval between stroke onset and sampling and could not affect infarct size on diffusion-weighted image. Castellanos et al[29] fitted logistic-regression after adjusting for confounders indicated that baseline caveolin-1 levels ≤0.17 ng/mL could predict symptomatic HT after cerebral ischemia independently. Zhang et al[30] also fitted logistic-regression and demonstrated that there were no significant differences concerning the levels of serum caveolin-1 between patients with silent lacunar infarcts and patients without, and that lower serum caveolin-1 level was associated with the presence of cerebral microbleeds.

Meta-Analysis Results

We used Egger's test to estimate publication bias. The publication bias may exist in Egger's test (p<0.05). Details of the meta-analysis results were shown in Figure 2. There was heterogeneity for the studies (Q=143.3778, p<0.05). The SMD (95% confidence intervals, CIs) between the control group and the stroke group was -0.5449 [-2.3344, 1.0000]. For the subgroup analysis, The SMD (95% confidence intervals, CIs) between the control group and the IS group was -1.4589 [-5.0129, 2.0951], and between the control group and the HS group was 0.3438 [-0.4140, 1.1017].

Discussion

Main Findings

In this meta-analysis, we pooled all eligible studies to analyze the association between caveolin-1 and stroke, with a sample size of 226 stroke cases and 487 control cases. We found that the ischemic stroke had higher serum Caveolin-1 level, and hemorrhagic stroke had lower serum caveolin-1 level than the control group. Overall, we found that higher serum caveolin-1 level may be associated with the stroke. However, those literature revealed that the stroke provokes the expression of the caveolin-1. Therefore, the evidence from those studies indicated that the caveolin-1 might play an important role in protecting stroke.

Important Viewpoints

Caveolae are flask-shaped invaginations in the plasma membrane 50 to 100 nm in diameter that lack a membrane-dense coat[20]. Caveolae have been implicated in a wide variety of cellular events, including transcytosis of proteins and cholesterol trafficking and more recently as signaling platforms that regulate diverse cellular processes[20]. Caveolin-1 is the main structural protein of caveolae and is involved in regulating signal transduction and cholesterol trafficking in cells[23]. Zhang et al[30] have suggested that caveolin-1 is involved in the regulation of lipoprotein transcytosis across endothelial cells and in the regulation of vascular inflammation and mitochondrial oxidative metabolism.

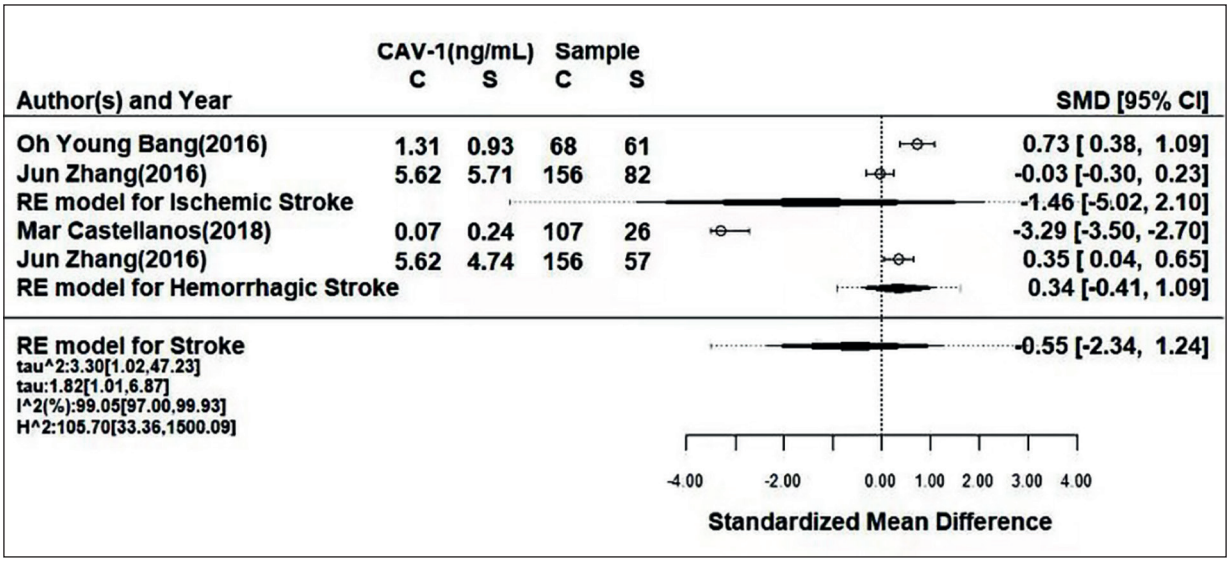

Figure 2. The forest graphs for the meta-analysis.

Caveolin-1 Suppressed Inflammatory Reaction

Hiromura et al[31] disclosed that caveolin-1 was a target molecule for DPP-4 inhibitors in the suppression of TLR4-mediated inflammation in mouse and human macrophages. Chang et al[23] found that caveolin-1 knockout mice had smaller injury volumes, milder neurologic deficits, less brain edema, and caveolin-1 plays a deleterious role in early brain injury after intracerebral hemorrhage, which suggested that the inhibition of caveolin-1 may provide a novel therapeutic approach for the treatment of hemorrhagic stroke. Yuan et al[32] used a respiratory infection model to reveal that caveolin-1 was critical for inflammatory responses regulating the STAT3/NF-0202B pathway and thereby impacting *Pseudomonas* aeruginosa infection. Feng et al[33] proved that caveolin-1 exerts its protective function by modulating inflammatory response, alleviating bacterial burdens, and suppressing thymocyte apoptosis.

Caveolin-1 Mediated Signaling Pathways

Matrix metalloproteinases (MMP) comprise a family of enzymes that cleave protein substrates based on a conserved mechanism involving activation of a site-bound water molecule by a Zn^{2+} ion[1]. Matrix metalloproteinase activity is regulated by a group of endogenous proteins called tissue inhibitor of metalloproteinases, which bind to active and alternative sites of activated MMP. Expression of caveolin-1 was downregulated in ischemic brains and the production of NO induced the loss of caveolin-1 in focal cerebral ischemia and reperfusion injury. Lakhan et al[1] revealed that caveolin-1 KO mice had higher rates of apoptotic cell death and larger infarction volumes than wild-type mice in an experimental ischemic stroke mode. Liu et al[2] found that the MMP-2 was the major enzyme mediating oxygen-glucose deprivation (OGD)-induced occludin degradation, and caveolin-1 was responsible for claudin-5 redistribution, which indicated that cerebral ischemia initiates two rapid parallel processes, MMP-2-mediated occludin degradation and caveolin-1-mediated claudin-5 redistribution, to cause BBB disruption at early stroke stages relevant to acute thrombolysis. Chen et al[34] demonstrated the feedback interaction among reactive nitrogen species, caveolin-1, and matrix metalloproteinases provides an amplified mechanism for aggravating ischemic brain damage during cerebral ischemia-reperfusion injury, which have shown potential for targeting to protect the brain in the ischemic stroke.

Caveolin-1 Prevented Peroxide Damage

Oxidative stress has been shown to play an important role in stroke progression, and reactive oxygen species were also generated intracellularly to serve as second messengers, and some are linked to caveolae signaling systems. Suchaoin and Chanvorachote[35] showed that overexpression of caveolin-1 significantly reduced reactive oxygen species and attenuated cell death. However, inhibition of caveolin-1 resulted in enhanced reactive oxygen species and cell death.

Caveolin-1 Plays a Pivotal Role in Reverse Cholesterol Transport

Cholesterol efflux is an important component of reverse cholesterol transport closely relating to the expressions of caveolin-1. When cholesterol levels or intracellular cholesterol levels are elevated, caveolin-1 is translocated to the endoplasmic reticulum, Golgi bodies, and endoplasmic reticulum or round-trip shuttle between caveolae and the Golgi body to transfer intracellular cholesterol to caveolae. Qin et al[5] pointed that caveolin-1 has a role in cholesterol accumulation and transcytosis when cells are incubated with ox-LDL. Li et al[36] studies also supported a role for caveolae in maintaining cellular cholesterol balance. Caveolin-1 is a high-affinity lipid binding protein, the expression of caveolin-1 is dramatically upregulated in aortas with perivascular adipose tissue transfer and involved in lipoprotein transcytosis. Sanon et al[37] indicated that caveolin-1 knockout mice suffer from pulmonary fibrosis and hypertension, and cardiac hypertrophy.

Conclusions

Our results revealed that the high levels of caveolin-1 were associated with the stroke, which may remedy the stroke. Besides, an opposite result was observed for the association of the caveolin-1 on the ischemic stroke and hemorrhagic stroke. To confirm this association, further studies are necessary. However, several limitations in this meta-analysis should be considered. In view of the influence of caveolin-1, the results would be more precise if the data coming from the model adjusted with some other variables associated with stroke, including age, smoking, coronary heart disease, hypertension, family history, and so on.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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