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Review article

Stroke-prone renovascular hypertensive rat as an animal model for stroke studies: From artery to brain

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ABSTRACT

High blood pressure is a main risk factor for both initial and recurrent stroke. Compared to the poststroke situation in normotension, the brain lesion is larger in hypertension, and the treatments may not be as effective. Thus, the results from healthy individuals may not be directly applied to the hypertensive. In fact, the high prevalence of hypertension in stroke patients and its devastating effect urge the necessity to integrate arterial hypertension in the study of stroke in order to better mimic the clinical situations. The first step to do so is to have an appropriate hypertensive animal model for stroke studies.

Stroke-prone renovascular hypertensive rat (RHRSP) introduced in 1998, is an animal model with acquired hypertension independent of genetic deficiency. The blood pressure begins to increase during the first week after constriction of bilateral renal arteries, and becomes sustained since around the 3rd month. Because the morphological and physiological changes of cerebral arteries are similar to those in hypertensive patients, the rats represent a higher than 60% incidence of spontaneous stroke. The animal model has several advantages: one hundred percent development of hypertension without gene modification, high similarity to human hypertension in cerebrovascular pathology and physiology, and easy establishment with low cost. Thus, the model has been extensively used in the investigation of ischemic stroke, and has been shown as a reliable animal model.

This paper reviewed the features of RHRSP and its applications in the treatment and prevention of stroke, as well as the investigations of secondary lesions postischemic stroke.

Contents

1. Introduction

Stroke is a major health issue worldwide because of its high incidence and morbid consequences. Blood pressure has been recognized as the most important risk factor of both initial and recurrent stroke, and approximately two thirds of stroke burden globally is attributable

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to nonoptimal blood pressure [1]. The insidious pathology alters the structure and function of cerebral arteries, exaggerating the vascular lesions in brain with the elevation of blood pressure level [2]. Indeed, the brain infarct poststroke is larger in hypertension compared to that in normotension, and the penumbra is smaller and disappears faster [3]. Even the treatment effective for the normotensive individuals may not be effective for the hypertensive individuals. For example angiotensin converting enzyme inhibition can reduce infarct in the normotensive rats but not in the hypertensive rats [4]. The high prevalence of hypertension in stroke patients and its devastating effect on the brain urge the necessity to integrate arterial hypertension in the study of stroke in order to better mimic the clinical situations. Therefore, the use of hypertensive animal models has become especially important.

The representative hypertensive animal models used in stroke studies are the stroke-prone spontaneously hypertensive rat (SHRSP) and stroke-prone renovascular hypertensive rat (RHRSP), both with high incidence of spontaneous stroke. SHRSP is a genetically inherited model with not only hypertension similar to human essential hypertension, but also complex neural disturbances that could be a parallel genetic phenomenon unrelated to the elevated blood pressure [5]. RHRSP is a renovascular hypertensive model independent of a genetic deficiency. Renovascular hypertension represents the second-leading cause of secondary hypertension, mainly among the elderly [6]. It has been proven that arterial lesions are similar in both essential and secondary hypertension [7]. Since RHRSP is an acquired stroke-prone hypertensive model without any known brain impairment caused by gene modification, it can be another promising animal model for stroke study. In this article, we aimed to review the model of RHRSP concerning its features and its application in the stroke studies.

2. Characteristic of RHRSP

2.1. History of renovascular hypertensive rat models

Early in 1934, Goldblatt, H. et al. introduced the renovascular hypertensive rat models that have been widely used thereafter, and the experimental renovascular hypertension was thus named as Goldblatt hypertension. It's well known that the rennin–angiotensin system (RAS) and neurogenic mechanisms interact in the development and maintenance of renovascular hypertension [8]. With the constriction of renal arteries, the enhanced synthesis of renin and angiotensin II acutely increases peripheral resistance and thus blood pressure. The responsiveness to angiotensin II in the central adrenergic system including rostral ventrolateral medulla, paraventricular nucleus and supraoptic nucleus is also enhanced [9]. A transgenic mouse model with selective AT_{1a} receptor overexpression in the brain stem showed accelerated hypertension, wherein the angiotensin II level was not only significantly increased in the plasma, but also in the brain stem and the hypothalamus even when the plasma level returned to normal, correlated with blood pressure level, revealing the key role of the central RAS in the development and maintenance of renovascular hypertension [10].

There are three renovascular hypertensive animal models: the one-kidney one-clip (1k1c), two-kidney one-clip (2k1c), and two-kidney two-clip (2k2c) models. In the 1k1c model, one kidney is removed and the left renal artery is constricted; in the 2k1c, both kidneys are preserved and one of the renal arteries is constricted; and in the 2k2c, both kidneys are kept and both renal arteries are constricted. It was found that the systolic blood pressure was persistently elevated since the 3rd week in all three models, but began to increase as early as 1 week postoperation only in 1k1c, and the peak of the blood pressure was highest in 2k2c [11].

2.2. The introduction of RHRSP

Zeng and his colleagues [11] introduced the renovascular hypertensive model of 2k2c as a stroke-prone model. In this model, when the rats were young (80–100 g), the roots of both renal arteries were exposed and constricted with ring-shape clips (0.3 mm in diameter). The blood pressure exceeded 150 mm Hg at the end of the 3rd week, then rose progressively to 180–220 mm Hg in about 3 months (Fig. 1), and gradually reached the platform of blood pressure of 200–240 mm Hg in around 6 months. Because the incidence of spontaneous stroke was more than 60%, the animal model of 2k2c has been named as stroke-prone renovascular hypertensive rats (RHRSPs). The mortality of RHRSP was about 10% until 12 weeks, but increased to 60% over a period of 34 weeks, mostly due to spontaneous stroke [11,12]. After 34 weeks, almost all rats survived.

The brain lesions develop over a time frame of 6–40 weeks postrenal artery constriction, including infarction (about 50%), hemorrhage (about 20%) and mixed stroke (about 30%) with lesions located mainly in the hemispheres, occasionally in the cerebellum or brain stem [11]. The mean time of onset was around 100 days, identical in the three different stroke subtypes. 90% of animals with spontaneous stroke presented neurological symptoms, only 10% showed no symptoms and stroke foci were found after euthanasia. In contrast, the incidence of spontaneous stroke was rather low in the other two types of renovascular hypertension models, with 23.3% in 1k1c and 16.7% in 2k1c (Table 1). The high incidence of spontaneous stroke is due to the pathological and physiological changes in cerebral vessels in RHRSP, which will be stated in the following session. Since the pioneer work of Zeng and his colleagues, RHRSP has been exclusively used in the study of stroke and related fields.

2.3. Cerebrovascular morphology and physiology in RHRSP

The pathology of cerebral vessels is similar to that in hypertensive patients. There are hyalinosis, fibrinoid necrosis, hyperplasia of internal or external layers (or both) of cerebral arterioles or small arteries with enhanced mural thickness and luminal stenosis [11]. Microaneurysms, disrupture of basal membrane and thrombotic vascular occlusions can also be found (Fig. 2). In addition, anastomotic branches between middle and anterior cerebral artery are reduced. Further, the lower limit of cerebral autoregulation was found to positively correlate with the mean artery blood pressure in RHRSP [13], similar to what happens in humans with long-term hypertension.

Previous studies have revealed that the exaggerated oxidative stress and enhanced ion channel activity are involved in the excessive cerebrovascular remodeling stated above. In RHRSP, the increased level of plasma angiotensin II contributes to the augmentation of oxidative stress in the vascular wall [14]. The reduction of oxidative stress by the inhibition of NAD(P)H oxidase with apocynin could diminish fibrosis, an important cause leading to vascular wall stiffness and remodeling, via reducing fibronectin level in cerebral vessels [15]. On the other hand, basilar artery in RHRSP underwent vascular remodeling with

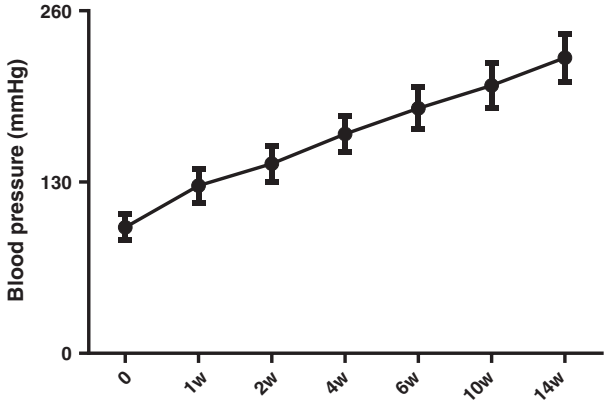

Fig. 1. The blood pressure of RHRSP before and after the constriction of bilateral renal arteries; n = 186.