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Research in Age Associated Diseases: Focus on Experimental Stroke

Sanaz Nasoohi*

Neuroscience Research Center, Shahid Beheshti University of Medical Science, Iran

*Corresponding author: Sanaz Nasoohi, Neuroscience Research Center, Shahid Beheshti University of Medical Science, Tehran, Iran, P.O. BOX: 19615-1178; Tel: +98(021)22429765-9; Fax: +98(021) 22432047; Email: sanaznasoohi@sbmu.ac.ir

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Aging is well defined as a failure to maintain homeostasis under conditions of physiological stress like the inevitable age associated disorders. Accordingly chronologic and biologic age are not well matched in all living organisms which is inclusive in term of "functional aging" and exemplified in young-onset Parkinson's disease. The inability for "keeping it together" settles in several organ systems leading to a variety of age associated disorders particularly in vital organs. There is increasing attempt in basic research to address age-associated disorders to eventually provide evidence-based approaches to health care system to improve life quality and expectancy. Countless animal models are developed to afford the requisite experimental tools to investigate the underlying intricate pathology and therapeutic targets for each age associated organ disease. Preclinical studies on cancer, renal failure, hepatic insufficiency, myocardial infarction, Alzheimer's disease and stroke are few instances of empirical investigations in the wake of providing therapeutic knowledge in elderly medicine. For some pitfalls however, the pile of even groundbreaking preclinical findings frequently fail to bring new approaches to geriatric medicine, at least partly explaining the improvidence of huge investment in translational research.

As of the leading cause of death and morbidity worldwide, stroke is among the intriguing research areas in elderly people requiring appropriate animal models for experimental examinations. Several stroke models with different technical approaches as well as translational values are available for researchers to address the specific hypotheses. Providing a direct observation on brain vessels, some involve craniotomy and gentle occlusion or cauterization of superficial cortical vessels. However many researchers opt for alternative models not impairing intracranial pressure which is directly involved in stroke induced injury. A less invasive model could be established through microinjection of vasoactive compounds like endothelin 1 in the vicinity of particular intracerebral vessels, requiring the precise targeting of intracerebral capillaries. The less invasive invented model so far appears to be photo-thrombotic occlusion of cerebral vessels which works through intra vascular clot formation with the aid of photosensitive dyes. This does not involve intricate surgery though, is not yet practically efficient to produce a defined penumbral region as the salvageable tissue to appropriately address potential therapeutics [1,2]. Alternatively, based on the existing statistics, many scientists in the field rather using intraluminal model in which the origin of middle cerebral artery (MCA) is blocked by introducing micro-bids or silicon coated microfilaments through internal common carotid artery. Named as MCA occlusion (MCAO) this method provides the advantages of simulating large number of occlusive strokes, mostly affecting MCA in the brain [3,4]. Blocking MCA by insertion of homologous blood clot represent the most clinically relevant available model engaging several components of immune system as well as coagulation haemostasis. Nevertheless embolic MCAO is of high translational value in stroke research, certainly yet it may not reflect many of age associated conditions in clinical practice.

In fact some comorbidities like hypertension, diabetes, and hyperlipidaemia are leading cause of complications in elderly people with stroke. As such, to provide more precise translation, more disease models are being incorporated into the stroke research design. Above all, hypertension as an independent basis for atherosclerosis, has been proven to be an almost absolute predictive covariate for stroke. That is almost about 60% of stroke patients have hypertension [5]. Spontaneously hypertensive rats (SHR) are therefore, among the most relevant species to the topic. Based on Scopus indexed papers, just around 20% of the preclinical research reports have used hypertensive animals in their experimental design. Diabetes indicating a poor prognosis in stroke patients, also exists in around 30% of patients with stroke [6]. That is while less than 1.5% of published works reflect diabetes as a studied comorbidity in stroke animals. Such statistics goes far below when it comes to renal dysfunction and hyperlipidemia which are highly ignored as of predominant deteriorating covariates, respectively existing in one third [7] and half [8] of stroke patients. Based on specific hypotheses of the study, choosing and reporting as well as executing appropriate disease models bring strengthening criteria to the preclinical conclusions which are comprehensively discussed elsewhere [9].

Even in the best matched comorbidities in experimental stroke in large animals, researchers have much to integrate their finding to geriatrics medicine. As defined aging is a complex modification in several system organs ending with less reservoir to interface stressful conditions which may dramatically influence physiologic responses to any external stimuli. At receptor levels besides alterations in downstream effectors, inconsistent upregulations or downregulations have been reported [10]. So that there is no cue to predict about potential drug-receptor affinity and interaction. It is a general belief that elderly are more responsive and susceptible to drugs effects or side effects. However this might be mostly ascribed to intense changes in kinetics of the drugs. Distribution of most of the exogenously administered compounds are remarkably altered for the altered body composition toward a less lean body mass as well as less protein binding sites in plasma [11]. For much of lipid soluble drugs including those developed for CNS diseases like stroke, this means higher values for apparent volume of distribution (Vd) and thus unpredictable half-life for the later redistribution. Interestingly often this does not concur with less plasma concentrations since much of the elimination machinery is helpless for the growing insufficiency of renal and hepatic function. On the other side, while exposed to water soluble agents, BBB in stroke elderly patients shows higher permeability not only for the deteriorating effect of ischemia but also for the proven impairment in tight junctions [12].

All of these evidences may objectively urge researchers to consider age-associated alterations while dealing with new therapeutics investigations for stroke. That is apparently no stroke research is comparable to those conducted in aged animals with its total unique features. With almost 10% of stroke

research reports conducted on aged animals there is a seemingly increasing trend toward more translation to the affected population by stroke. However, the venue for optimization is endless as screening and sorting the aged animals based on the randomly developed comorbidities may further provide utterly accurate lines for final conclusions.

Divergence of Findings in Young Adult and Aged Stroke Animals

Atherosclerosis appeared to be an important pathogenic cause of all age populations [13]. Brain infarcts have been shown to develop more rapidly in aged rats but in the following days it might come to similar sizes in both ages [14]. Interestingly there are some evidences implying the response of the aged rat brain is qualitatively different from the young but not quantitatively [15]. Meaning aged rats had great difficulty in rising a timely response to stroke in terms of gene reprogramming, this well exemplifies sort of inability to confront stress. Given age is generally believed to parallel with reduction of angiogenesis and neurogenesis, some tropic factors and cell therapy approaches have been shown to produce rather pronounced alleviation in aged animals, suggesting that aging-related microenvironment does not preclude the due advantages [16]. In fact recent findings suggest that the cortices of aging brain has considerable more plastic capacity to keep its function following focal cerebral insults [17]. Conspicuously, aged animals may demonstrate dramatic differences from young animals in response to potential therapeutics. Instantly in aged stroke animals MK-801 (NMDA receptor antagonist) is not efficient as much as in young animals [18], while aged animals benefit much more from adiponectin administration [19]. The contradictory result might bring substantial concerns on translational value of inappropriate animal models to interpret about underlying research hypothesis.

Conclusion

Elderly people are much vulnerable to develop emboli both for augmented coagulators and fractions following falls and osteoporosis. Furthermore the hemodynamic response of corresponding patients to thrombolytic therapy and associated hemorrhagic events is largely un-investigated. Stroke research while conducted on aged animals could be more accurately translated to the particular affected age group in human. Nevertheless, still there are several age associated features could not be easily addressed in aged animals, including pharmacogenomics, patient compliance and multi-medication as of serious concerns in elderly people. Relatively higher mortality rate and more costs may act as limiting factors, addressing research hypothesis in aged animals is worth efforts for getting to high translational value. This might be utterly facilitated by innovation of animal models of aging through genetic modulations instantly through manipulating clock genes ending with early aging.

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