Neuropharmacology xxx (2017) 1–8

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise

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ARTICLE INFO

Article history:
Received 11 July 2017
Received in revised form
12 August 2017
Accepted 17 August 2017
Available online xxx

Keywords:
Hypothermia
Cooling
Stroke
Ischemia
Cerebral infarct
Infarction

ABSTRACT

Therapeutic hypothermia, or cooling of the body or brain for the purposes of preserving organ viability, is one of the most robust neuroprotectants at both the preclinical and clinical levels. Although therapeutic hypothermia has been shown to improve outcome from related clinical conditions, the significance in ischemic stroke is still under investigation. Numerous pre-clinical studies of therapeutic hypothermia has suggested optimal cooling conditions, such as depth, duration, and temporal therapeutic window for effective neuroprotection. Several studies have also explored mechanisms underlying the mechanisms of neuroprotection by therapeutic hypothermia. As such, it appears that cooling affects multiple aspects of brain pathophysiology, and regulates almost every pathway involved in the evolution of ischemic stroke. This multifaceted mechanism is thought to contribute to its strong neuroprotective effect. In order to carry out this therapy in optimal clinical settings, methodological and pathophysiological understanding is crucial. However, more investigation is still needed to better understand the underlying mechanisms of this intervention, and to overcome clinical barriers which seem to preclude the routine use therapeutic hypothermia in stroke.

Contents

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http://dx.doi.org/10.1016/j.neuropharm.2017.08.025
0028-3908/

1. Introduction

Since Busto and colleagues (Busto et al., 1987) demonstrated that lowering of brain temperature by only a few degrees could ameliorate neuronal death in 1987, there has been continuous renewed interested in this robust neuroprotective effect. Therapeutic hypothermia has been widely to be one of the most reliable neuroprotective therapies for several cerebral disorders and injuries (van der Worp et al., 2007; Yenari and Han, 2012), including stroke, traumatic injury, global ischemia after cardiac arrest, and hypoxic-ischemic encephalopathy.

Stroke is one of the leading causes of death and disability in this industrialized world. Of these, approximately 87% of all strokes are ischemic (Liu et al., 2016). Despite such high prevalence, there is no proven effective therapy, other than the revascularization within a limited time window. However, due to its restricted time window, patients who can receive such intervention is limited. Based on numerous reports demonstrating that therapeutic hypothermia can provide robust neuroprotection, this therapy has the potential to be one of the most attractive therapies for ischemic stroke (van der Worp et al., 2007; Yenari and Han, 2012). Prior clinical trials showed that hypothermia improved clinical outcomes in comatose survivors of out-of-hospital cardiac arrest (Bernard et al., 2002) and neonatal hypoxic ischemic encephalopathy (Perrone et al., 2010; Tsuda et al., 2017).

To date, numerous pre-clinical studies have shown that cooling affects multiple pathways at various stages of ischemic stroke (Yenari and Han, 2012). During the acute stage of ischemia, decreases in cerebral blood flow disrupts ionic homeostasis, leading to increased intracellular calcium and release of excitatory neurotransmitters. Increased intracellular calcium also causes downstream effects such as mitochondrial dysfunction, leading to increased reactive oxygen species (ROS) generation (Gonzalez-Ibarra et al., 2011). In the sub-acute stage, apoptotic and inflammatory pathways are initiated hours to days later (Ceulemans et al., 2010). Once initiated, these pathways lead to neuronal cell death through a combination of apoptosis, inflammation, oxidative stress, and excitotoxicity pathways. Therapeutic hypothermia is thought to affect almost every one of these pathways (Yenari and Han, 2012). This multifaceted mechanism is thought to explain its strong therapeutic effect (Yenari and Han, 2012). Thus, it is likely that no single factor can explain its underlying protective effect (Yenari and Han, 2012).

Since therapeutic hypothermia is a promising and attractive therapy for ischemic stroke, a precise understanding of what is known and what is unknown is important. This will allow the optimization and standardization of any future clinical trials, and will provide bench researchers future direction for further preclinical work. This review mainly focuses on animal studies of therapeutic hypothermia and ischemic stroke. We will first discuss the optimal cooling conditions which might be effective both in experimental models and human stroke. We will also discuss cellular and molecular pathways affected by cooling. Cumulative knowledge may prove helpful to the effective translation of therapeutic hypothermia to clinical settings.

2. Methodological aspects of therapeutic hypothermia

Most pre-clinical studies of hypothermia use small rodent models. In rodents, cooling is performed by applying a cooling blanket or by spraying water or alcohol on the animal's fur. Unlike humans, target temperatures can be reached within minutes and maintained with reasonable control in the anesthetized animal. Rewarming requires placing the animal on a warming blanket with a heat lamp suspended over the animal. Rewarming takes a similar amount of time as cooling, and no obvious detrimental effects have been reported when this approach is used in small animal models. This is in contrast to what is seen at the clinical level where cooling requires several hours as does rewarming. Further, too rapid rewarming runs the risk of increased brain edema and intracranial pressure (ICP). Cooling for longer durations (that is, for more than 1day) in awake and freely moving animals can be accomplished by using automated misting systems and overhead fans and appear to be well tolerated to temperatures of 32 °C (Colbourne et al., 1996).

A novel method to induce hypothermia in rodents was reported recently (Lamb et al., 2016), where hypothermia was attained by cooling circulating blood at the inferior vena. This approach may complement traditional surface cooling methods, because of its more rapid induction and tighter regulation of temperature.

2.1. Optimal cooling conditions

In animal studies of hypothermia in ischemic stroke, a wide range of depths, durations, and delays to initiation of cooling has been studied (van der Worp et al., 2007). Because optimization of these methodological parameters is crucial for clinical application, several studies had been carried out in various stroke model rodents. Previous work and meta-analyses (Krieger and Yenari, 2004; van der Worp et al., 2007) revealed that relatively small decreases in brain temperature are as protective as lower temperatures. In fact, brain temperatures in the range of 30–34 °C (decreased from normal body temperatures of 36–38 °C) seem to provide protection that is as robust as temperatures below 25 °C. Timing and duration are also important factors involved in achieving neuroprotection induced by therapeutic hypothermia. Early initiation and long duration increase the probability of a good outcome (Kurisu et al., 2016a; Yenari and Han, 2012). Previous meta-analyses showed that the therapeutic efficacy induced by hypothermia was best with lower temperatures, and when treatment was started before or at the onset of ischemia (van der Worp et al., 2007). Furthermore, there appeared to be a small correlation between longer durations of cooling and decreased infarct size (van der Worp et al., 2007). Neuroprotection can also be attained even when cooling is delayed, provided decreased temperature is maintained for long durations (24–48 h) (Yenari et al., 2008). This remarkable effect suggests the promise of hypothermic therapy for clinical ischemic stroke. However, at present, the long-term effect of therapeutic hypothermia is not fully clarified yet. Only a few preclinical studies (Colbourne et al., 1999; Maier et al., 2001) have demonstrated the durability of the effect to be at least a few months.

Although cooling can be easily achieved in small rodents, it brings substantial challenges in humans. Considering the issues

Please cite this article in press as: Kurisu, K., Yenari, M.A., Therapeutic hypothermia for ischemic stroke; pathophysiology and future promise, Neuropharmacology (2017), http://dx.doi.org/10.1016/j.neuropharm.2017.08.025