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Cerebral Ischemia and Post-Ischemic Treatment with Hypothermia

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1. Introduction

With its strict dependence on a continuous supply of oxygen and glucose to meet its energy needs and its high metabolic rate, the brain is particularly sensitive to any compromise of blood supply. Brain ischemia, as occurs in a number of disease states but most importantly in ischemic stroke and during cardiac arrest, rapidly results in exhaustion of ATP, triggering an energy crisis. Within minutes, the failure of ion pumps sees the depolarisation of neuronal cell membranes and the consequent release of stored presynaptic glutamate, leading, by way of overstimulation of glutamate receptors (=excitotoxicity), to many-fold increases in intracellular calcium and zinc concentrations. Severely affected cells die within only a few minutes. In those cells that are less severely injured, ongoing cellular and tissue damage occurs due to activation of proteolytic enzymes, oxidative and nitrosative stress (Forder & Tymianski, 2009), altered calcium homeostasis, initiation of active cell death pathways (apoptosis, necrosis, autophagy and necroptosis), inflammation (microglia and astrocyte activation, neutrophil infiltration within 4 - 6 hours), cortical spreading depressions, disruption of the blood brain barrier (BBB; starting at 2 hours, followed by a second phase from 24 - 72 hours; Brouns & De Deyn, 2009), microvascular injury (which promotes BBB disruption, inflammation and impairs vascular control of blood flow), hemostatic activation (platelet activation and the intrinsic pathway) and edema. Additionally, though reperfusion is the cornerstone of treatment, when/if it is established, many of these damaging events can be exacerbated.

These processes are interconnected, rather than sequential, and presenting them as a list might be misleading if it were to be taken that counteracting one event would therefore prevent those occurring later in the list, even if they do in fact occur later in time. The list only acts as a summary of the damaging events, against which can be checked the likelihood of a potential therapy to do some good. The importance of each process waxes and wanes at different times during and after the ischemic episode, so an important principle of effective therapy is that it will need to be applied at the time of the injurious events to counteract its effect. In many respects hypothermia is, in theory, the ideal therapy, with multiple mechanisms of action in opposition to the consequences of ischemia.

2. Background of therapeutic hypothermia

Cooling of the body for therapeutic purposes is not a new concept in medicine. For example, in 1941 the British Medical Journal noted that generalised therapeutic hypothermia was under investigation for the treatment of various cancers, such as bladder carcinoma (Anonymous, 1941). It was also suggested that whole body cooling might find use in patients with intractable pain, morphine addiction, leukaemia, and schizophrenia, though no mention was made at this time of stroke or cardiac arrest. In the early 1950s, however, studies were being performed in which animals were cooled to very low temperatures (16 - 19^{o}C in macacus rhesus monkeys, 2.5 - 5^{o}C in groundhogs) to permit cardiac surgery (Bigelow & McBirnie, 1953). Cardiac output was completely stopped in these experiments for long periods (15 - 24 minutes in the monkeys, 1 - 2 hours in the groundhogs) with few deaths, and no apparent neurological deficits when the animals were recovered.

Thus, it has been known for several decades at least that a state of hypothermia decreases central neurological injury in the face of ischemia. This has led to many animal studies, of various designs, which have tended to confirm the potential for hypothermia to reduce ischemic brain damage (for review see Meloni et al., 2008). In recent years, clinical trials have proven that moderate hypothermia, using a target body temperature of 33^{o}C, improves outcomes for cardiac arrest survivors (Bernard et al., 2002; Hypothermia after cardiac arrest study group, 2002; Meloni et al., 2008), and its use is, at the time of writing, under investigation in several ongoing or planned trials following ischemic and hemorrhagic stroke (Table 1; Meloni et al., 2008). Between them, these studies will answer several of the important questions regarding the best use of therapeutic hypothermia.

Study*	**Method of cooling**	**Number of subjects**	**Delay from stroke onset**	**Tempe-rature**	**Duration**
Cerebral hypothermia in ischemic lesion (CHIL). Stroke Trials Directory	Cold infusion induction + endovascular cooling or local head cooling	80	Within 6h	33°C	24h
Cooling in acute stroke-II (COAST-II). Stroke Trials Directory	Cold infusion induction + endovascular cooling#	50	Within 3h; 30 - 90min after tPA	35°C	24h
Mild hypothermia in acute ischemic stroke (MHAIS) Stroke Trials Directory	Surface cooling#	36	Within 6h	35°C	12h
Mild hypothermia in acute ischemic stroke trial – Edinburgh (HAIST-E). EUROHYP	Cold infusion induction + surface cooling#	24	Within 4.5h	35 or 33°C	12 or 24h

Study*	Method of cooling	Number of subjects	Delay from stroke onset	Tempe-rature	Duration
Cooling for ischemic stroke trial (COOLIST); NTR2616. Nederlands Trial Register	Cold infusion induction + surface cooling#	84	Within 4.5h	35, 34.5 or 34°C	24h
Mild hypothermia in acute ischemic stroke (MASCOT; Pilot). EUROHYP	Surface cooling	40	Within 24	33°C	24h
Mild hypothermia in acute ischemic stroke: surface. vs endovascular cooling (HAIS-SE). Stroke Trials Directory	Cold infusion induction; surface or endovascular cooling #	60	Within 4.5h; 30min after tPA	34°C	12, 18 or 24h
Cooling in intracerebral hemorrhage (CINCH). EUROHYP	Endovascular cooling	50	Within 6 - 18h	35°C	8 d
Hypothermia for intracerebral hemorrhage. Clinical Trials	Surface cooling	20	Within 6h	34°C	24h
European stroke research network for hypothermia (EuroHYP). EUROHYP	Cold infusion induction + surface or endovascular cooling#	1500	Within 6h; within 90min after tPA	34 - 35°C	24h

* For more detail see Stroke Trials Directory, EUROHYP Nederlands Trial Register and Clinical Trials web sites (details provided in reference list). # Patient awake and treated with pethidine and/or buspirone to control shivering and improve comfort.

Table 1. Current clinical trials of hypothermia in stroke (ischemic and hemorrhagic).

3. Neuroprotective mechanisms of hypothermia

There is evidence that therapeutic hypothermia has beneficial effects by numerous mechanisms including reduction of metabolic rate, promotion of energy recovery after ischemia, inhibition of glutamate release, inhibition of cell death pathways, inhibition of free radical formation, inhibition of inflammation, preservation of the BBB, stimulation of neurotrophin expression, and numerous effects on molecular responses to ischemia (e.g., inhibition of AMPK and MAPK activation, inhibition of SMAC/Diablo, p53).

Intuitively, a reduced metabolic rate might be expected to be one of the more important means by which hypothermia could protect against ischemia, and it does make a contribution, though the effect is easily overestimated. It has been calculated that, on the measure of reduced metabolic oxygen consumption, 5 minutes of ischemia at 37^{o}C would cause approximately equivalent damage to 15 minutes of ischemia at 27^{o}C (Schaller & Graf, 2003). Thus, the benefit is only moderate even at substantially lower temperatures than are usually considered suitable for most therapeutic purposes. There is evidence, however, that hypothermia also expedites the recovery of ATP stores after a period of ischemia, as well as improving the return of energy metabolism to pre-ischemic levels (Erecinska et al., 2003; Zhao et al., 2007). The combination of reduced demand and improved recovery both during and after what is a state of failed energy supply is perhaps enough to explain the outstanding neuroprotection afforded by intraischemic hypothermia. That is, without taking into account any of its other actions, hypothermia reduces the severity of any one incidence of cerebral ischemia. Its influence does not end there, however, though clearly hypothermia will necessarily be less effective when delayed.

While excitotoxicity, principally attributable to overstimulation of the NMDA subtype of glutamate receptor, is a critical component of the ischemic cascade, its very early occurrence means it is likely to remain a frustrating target for therapeutic intervention. That said, there is fair evidence that hypothermia reduces, or at least delays, the release of glutamate from ischemic neurons, probably by delaying the onset of anoxic depolarisation (Zhao et al., 2007). Using a cardiac arrest model, it was shown that hypothermia (31^{o}C/20min) either during ischemia or initiated at the time of reperfusion reduced extracellular glutamate concentrations (measured at the hippocampus), but not when the initiation of hypothermia was delayed by as little as 5 minutes after reperfusion (Takata et al., 2005). Hachimi-Idrissi et al. (2004) found a long lasting (more than 2 hours) inhibition of both glutamate and dopamine release in hypothermia (34°C/1h) treated animals when commenced after resuscitation in an asphyxiation/cardiac arrest model.

Importantly, the activity of hypothermia in reducing oxidative damage after ischemia or ischemia-like insults is well-supported. Shin et al. (2010) found that, in rats, the death of neurons induced by hypoglycemia could be reduced by maintaining brain temperature at 33 - 34^{o}C for 1 hour, and that this was associated with reductions in zinc ion release/translocation, generation of ROS, and activation of microglia. Maier et al. (2002) reported that intra-ischemic hypothermia (33°C/2h) reduced production of the superoxide anion after transient focal cerebral ischemia, and Van Hemelrijck et al. (2005) showed that hypothermia (34°C/2h during ischemia) reduced hydroxyl radical formation, by inhibition of neuronal NOS, during the resuscitative phase after focal cerebral ischemia.

There is general agreement from several studies that hypothermia improves membrane stability, reducing disruption of the BBB as well as protecting neuronal cell membranes. Kiyatkin and Sharma, 2009, found that hypothermia at 34 - 35ºC in normal brains slightly increased BBB permeability to albumin (compared to normothermia), but this did not result in edema. The mechanism appears to be related to temperature dependent variations in the sodium and chloride content of brain tissue, such that hypothermia reduces these ions by an undescribed mechanism, preventing osmotic draw into this tissue and producing a relative dehydration. In any case, the effect was mild, certainly compared to hyperthermia, which markedly increased both BBB permeability and edema. Baumann et al. (2009) found, on the other hand, that after global ischemia hypothermia (32ºC/6h commencing after reperfusion) stabilised blood vessels and decreased BBB permeability, probably by preservation of the basement membrane. Nagel et al. (2008) measured extravasation of MRI contrast agent after transient focal ischemia (tMCAO), and found that hypothermia (33ºC/4h starting 60min into 90min MCAO) greatly reduced BBB disruption. Huang et al. (1999) showed that hypothermia (29°C/6h commencing after reperfusion) particularly reduces the second phase of BBB disruption that occurs around 24 hours after transient focal ischemia.

Besides these non-specific harmful processes, there are in the penumbra a variety of pro-apoptotic responses to ischemia that are mediated by particular molecular pathways. Identifying these pathways and investigating interventions to counteract them is a field of substantial current activity. There is too much to summarise here, and any such attempt would be likely to be out of date very soon. Nevertheless, a couple of examples are useful to give the flavour of the work being done, but for more additional information see recent reviews by Zhao et al. (2007) and González-Ibarra et al. (2011).

AMP-activated protein kinase (AMPK) is responsive to energy stress, and, when phosphorylated, suppresses anabolic and promotes catabolic activity, evidently in order to maintain ATP supplies. Perhaps paradoxically, AMPK inhibition reduces ischemic brain damage, and there is evidence that hypothermia (32ºC/6h commencing after reperfusion) inhibits AMPK activation after transient focal cerebral ischemia in mice (Li et al., 2011). Li & Wang (2011) demonstrated that hypothermia (33ºC during transient focal ischemia) reduced expression of the protein complex second mitochondrion-derived activator of caspases (SMAC), an important molecule in the activation of apoptosis, which is upregulated in response to a variety of insults. The reduction in SMAC expression was also associated with reduced neurological impairment in rats after focal ischemia.

4. Hypothermia and glial cells

The best neurological outcomes will be achieved by measures taken to address the consequences of ischemia not just in neurons and the BBB, but in glial cells as well. Studies of the effects of hypothermia on glia are relatively few, but those there are suggest that hypothermia promotes survival and inhibits pathological responses in microglia and astrocytes. Hypothermia does reduce activation and proliferation of microglia, thus reducing oxidative and nitrosative stress (Si et al., 1997). Reduced activation of microglia associated with hypothermia has been demonstrated by several studies using different animal models, for example, during and after global cerebral ischemia (Kumar and Evans, 1997; Webster et al., 2009), after transient focal cerebral ischemia (Inamasu et al., 2000), and after hypoxia/ischemia (Fukui et al., 2006). Hachimi-Idrissi et al. (2004) found that astrocyte

proliferation is also inhibited by hypothermia after asphyxiation/cardiac arrest and resuscitation. Haun et al. (1993) found that astrocyte cultures were made relatively resistant to an *in vitro* glucose-oxygen deprivation injury by hypothermia.

5. Depth of hypothermia

The efficacy of hypothermia increases as the depth of hypothermia increases, though the response is not linear. In a large meta-analysis of animal studies, van der Worp et al. (2007) found that the greatest therapeutic response (reducing mean infarct volumes by approximately 55%) was achieved by cooling to below 30ºC, though cooling to even 35ºC, the highest level of hypothermia included, still resulted in a considerable positive response (infarct volume reduction of 30%). What's more, the adverse effects of the treatment (specifically cardiac arrhythmias, coagulopathies and immunosuppression) also increase with increasing depth, as do the technical difficulties involved in bringing patients to deeper body temperatures in the first place. Therefore, the optimum target will be the best balance between therapeutic effect versus detrimental effect versus practicality. While the optimum target temperature is still to be determined, based on preclinical and clinical studies it will probably be in the range 33 to 35ºC, that is, what is usually referred to as moderate or mild hypothermia. As mentioned earlier hypothermia at 33°C is being used following cardiac arrest in comatose survivors admitted to intensive care wards. However, from a clinical standpoint, hypothermia of 35°C offers the advantage of being achievable in awake subjects outside of intensive care units, which would comprise the majority of stroke patients. Furthermore several of the ongoing and planned stroke trials listed in Table 1 will provide data that aims to specifically address the question of the relative efficacy of hypothermia at 33°C versus 35°C.

It is worth considering here the use of hypothermia during (when it is most effective) cardiothoracic and neurosurgical procedures, in which body temperatures are lowered from anywhere from 26 - 35°C, specifically to protect tissues, including the brain, during an anticipated period of compromised blood supply. For example during cardiac surgery, there are two distinct levels of hypothermia that are commonly used; a target body temperature of 34 - 35ºC is now becoming accepted as the standard for Cardiopulmonary Bypass (CPB), while in especially critical cases surgeons may opt to use Deep Hypothermic Circulatory Arrest (DHCA) in which patients are cooled to a rather extreme 15 - 26ºC (Choi et al., 2009; Cook, 2009; Mackensen et al., 2009).

6. Timing and duration of hypothermia

As noted earlier, the pathophysiology of cerebral ischemia is dynamic and multifaceted, with numerous damaging mechanisms occurring, becoming important at different times, and lasting for different durations, many of which interact to exacerbate the effect of another. It is an oversimplification to say that hypothermia reduces the impact of all of these damaging processes, but it's fair to say that that is the trend. Consequently, the earlier hypothermia is commenced and the longer it is maintained while the ischemic damaging processes are occurring will permit the greatest neuroprotective effect. This contention is, however, not particularly well borne out by the evidence from animal trials (van der Worp et al., 2007), though there are some possible reasons for this finding (van der Worp et al.,

2010). In the bulk of animal trials, hypothermic treatment is used during or very soon after ischemia, when it is most effective. Prolonging hypothermia in this situation allows little opportunity to improve on the highly effective neuroprotection afforded by early treatment, while permitting the adverse effects of hypothermia treatment (eg. coagulopathies, immunosuppression, pneumonia) to become significant. Furthermore, there will be a time after ischemia where delayed hypothermia will not be effective at inhibiting neuroregenerative processes. There is evidence, however, that the longer treatment is delayed, short periods of hypothermia have little or no effect, while prolonged hypothermia (>24h) can be very effective (Clark et al., 2008; Colbourne et al., 1999ab; Zhu et al., 2005).

Again, however longer treatment consumes more resources and also increases the health risks, particularly in patients who require sedation or anaesthesia to maintain the hypothermic state. The optimum duration of hypothermia will most likely be in the range 12 - 48 hours, and is likely also to be dependent on factors such as the specific cause of ischemia (stroke, cardiac arrest), severity of ischemia, age of patient and the time delay to commencing hypothermia after ischemia. In terms of therapeutic window, this will vary depending on the type of ischemia (focal vs global) and severity, but could be up to 6 hours following stroke (focal ischemia; Ohta et al., 2007) and up to 12 hours following global ischemia (Colbourne et al., 1999b; Coimbra & Walsh, 1994). With respect to rewarming it is becoming increasingly accepted that slow rewarming at the rate of 0.2 - 0.3°C/hour is most desirable (Bardutzky & Schwab, 2007; Bernard & Buist, 2003).

7. Cooling methods

One of the most significant barriers to therapeutic hypothermia is the technical difficulty involved in inducing the target temperature in the target tissue in a timely and safe manner. Large mammals such as humans are very efficient at maintaining a normal body temperature in the face of attempts to cool the body. Available techniques are surface cooling by refrigerative blankets, cooling helmets, cold air blowers, intravascular heat exchangers, intravascular cold fluids and, which is currently under investigation, intranasal evaporative cooling (Castrén et al., 2010; Jordan & Carhuapoma, 2007). An alternative approach is the use of pharmaceutical agents, such as the neurotensin analogue NT77 to alter the body's temperature set-point as monitored and controlled by the hypothalamus, thus allowing an effectively physiological induction of hypothermia (Katz et al., 2004). Each of these has advantages and disadvantages in cost, accuracy, degree of control, rate of cooling and ease of application. Mild hypothermia can be induced in awake patients, as long as steps are taken to manage the associated discomfort (see below), but moderate to deep hypothermia requires sedation or anaesthesia with intubation, ventilation and intensive care measures.

At present the intravenous infusion of cold salt solutions (4°C) at a rate of 20 - 30ml/kg over 20 - 30 minutes is gaining acceptance as the method of choice to induce hypothermia (Bernard et al., 2003; Polderman et al., 2005; Moore et al., 2008). The cold saline infusion procedure has several attractions as it is: i) inexpensive ii) safe; iii) relatively straight forward; iv) fast at inducing mild to moderate hypothermia (33 - 35°C); v) applicable in the field allowing early hypothermia induction; vi) suited for use in both comatose and awake subjects; and vii) often indicated anyway as a means of improving physiological parameters (blood pressure, renal function, acid-base homeostasis; Bernard et al., 2003). Following

hypothermia induction by cold saline infusion one or more of the cooling procedures outlined above would then be implemented to provide a more precise control of body temperature.

To further aid the induction and maintenance of hypothermia the use of pethidine (meperidine) alone or with other agents, such as, the anxiolytic buspirone or magnesium are being used (Kliegel et al., 2007; Mokhtarani et al., 2001; Martin-Schild et al., 2009; Zweifler et al., 2004; Table 1). The use of these agents, along with simple measures such as warm gloves and socks is especially useful when inducing hypothermia in awake patients to minimize discomfort and shivering (Mahmood & Zweifler, 2007).

8. Combination with other treatments

A substantial advantage of hypothermia is that it presents little or no obstacle to the application of other treatments, and in fact has been shown to enhance or act synergistically with some other neuroprotective approaches (Campbell et al., 2008; Zhu et al., 2005). In reviewing the literature, we have found that hypothermia in combination treatments generally has additive or synergistic effects, and in several instances medications which were thought to be neuroprotective were later found to induce hypothermia and in fact were not neuroprotective at all when normal body temperatures were maintained (Campbell et al., 2007; Nurse & Corbett, 1996). It is especially important that any potential stroke treatment should be compatible with tPA thrombolysis, and in this respect it appears based on *in vitro* data that at least for mild hypothermia (i.e. 35°C), it will not significantly reduce the effectiveness of tPA (Schwarzenberg et al., 1998; Shaw et al., 2007; Yenari et al., 1995).

9. Concluding remarks

There is compelling experimental and clinical evidence that mild to moderate hypothermia is effective following global and focal (ischemic stroke) cerebral ischemia. However, it is likely that the depth and duration of hypothermia that provides the best benefit to patients will vary depending on the type (global vs focal) and severity of brain ischemia, the time that hypothermia is commenced, and patient age and presence of co-morbidities (diabetes, hypertension). Therefore further experimental and clinical trials will be required to determine hypothermia protocols that best suit individual patients. Moreover, based upon the available human studies, it appears that the use of hypothermia, in particular mild hypothermia (35°C) is feasible and safe to implement in clinical situations. In addition, based on current information therapeutic hypothermia should be commenced as soon as possible after the ischemic event, and maintained for durations of 12 - 48 hours to achieve a sustained benefit in terms of neuronal recovery and survival and functional benefits. To this end, future experimental studies in global and focal ischemia models and the results of the clinical stroke trials, will no doubt, help address further refinement of therapeutic hypothermia protocols to better suit individual cases. In addition, evaluation of the effectiveness of hypothermia in combination with other potential neuroprotective agents such as magnesium, caffeinol, glutamate antagonists and anti-oxidants could further improve efficacy.

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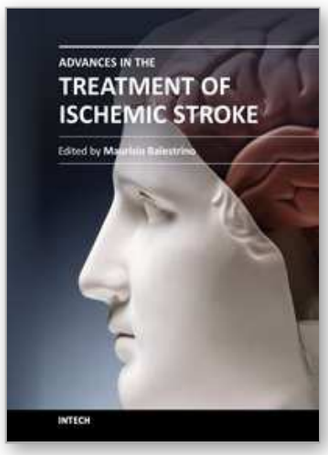

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In recent years research on ischemic stroke has developed powerful therapeutic tools. The novel frontiers of stem cells therapy and of hypothermia have been explored, and novel brain repair mechanisms have been discovered. Limits to intravenous thrombolysis have been advanced and powerful endovascular tools have been put at the clinicians' disposal. Surgical decompression in malignant stroke has significantly improved the prognosis of this often fatal condition. This book includes contributions from scientists active in this innovative research. Stroke physicians, students, nurses and technicians will hopefully use it as a tool of continuing medical education to update their knowledge in this rapidly changing field.

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