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Review

The actions of hyperthermia on the autonomic nervous system: Central and peripheral mechanisms and clinical implications

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ABSTRACT

Hyperthermia is defined as an elevated body temperature due to failed thermoregulation. It can occur under physiological conditions such as intense exercise or due to pathology such as malignant hyperthermia and heat stroke. It has also been implicated as a cause for sudden infant death syndrome. High temperatures are also used in medical interventions — hyperthermic chemotherapy or radiofrequency ablation, for example, which have serious side effects. The effect of hyperthermia on the central nervous system has not been fully researched, but even less is known on the effects of hyperthermia on the peripheral autonomic nervous system. In this review we discuss how conditions such as malignant or therapeutic hyperthermia affect the central and peripheral components of the autonomic nervous system, smooth muscle, skeletal muscle and cardiac muscle. We conclude that there is sufficient evidence for the detrimental effect of hyperthermia on central nerves, and that these effects are long lasting, although the major mechanism for this remains unknown. Similarly, the direct damage of hyperthermia to the enteric nerves also seems to be long lasting. In contrast, the reduced contractility of cardiac muscle and gastrointestinal smooth muscle when exposed to hyperthermia is short-lived. The consensus is that inadequate calcium handling is the mechanism of heat damage to cardiac and skeletal muscle. There is no such consensus when dealing with smooth muscle. The mechanism of hyperthermic damage to autonomic end organs such as the gastrointestinal tract has yet to be elucidated and further research into both central and peripheral hyperthermia is necessary.

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1. Introduction

Hyperthermia is defined as an elevated body temperature due to failed thermoregulation — a body temperature of greater than 37.5–38.3 °C in humans (Axelrod and Diringer, 2008; Laupland, 2009). Hyperthermia can occur under physiological conditions such as intense exercise; under numerous pathological conditions such as heat stroke and sepsis, or as result of medical intervention (Bouchama and Knochel, 2002; Eyer and Zilker, 2007).

Malignant hyperthermia (MH) is a rare life-threatening condition that is often inherited as an autosomal dominant disorder. It is usually triggered by exposure to certain drugs used for general anaesthesia; specifically, the volatile anaesthetic agents and neuromuscular blocking agents. In susceptible individuals, these drugs can induce an uncontrolled increase in skeletal muscle oxidative metabolism, which impedes thermoregulation, eventually leading to death if not treated quickly. MH is usually revealed by anaesthesia, or when a family member develops the symptoms.

Heat stroke is defined as a body temperature of greater than 40.6 °C due to environmental heat exposure with lack of thermoregulation. Substances that inhibit cooling and cause dehydration such as alcohol, caffeine, stimulants, medications, and age related physiological changes, predispose to classic heat stroke. Exertional heat stroke can happen in young people without health problems or medications, most often in athletes. Sudden infant death syndrome (SIDS) is the sudden, unexplained death of an infant under 1 year. It is of unknown aetiology, but as elevated room temperature, high infant body temperature and excess swaddling are known risk factors, it had been thought that hyperthermia might be a cause. These conditions will be discussed in this review, in conjunction with both how the autonomic nervous system is implicated in the aetiology, and how it is affected by these conditions.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a therapeutic modality that gained wide acceptance for peritoneal surface malignancies in cancer centres worldwide (Sugarbaker et al., 1989; Kuhn et al., 2002; Sarnaik et al., 2007; Hagendoorn et al., 2009; Piso et al., 2009; Yan et al., 2009). An important and common side-effect of this treatment is ileus (decreased motility of gastrointestinal (GI) smooth muscle — in this case, with a non-mechanical aetiology), for up to 15–35 days (Esquivel et al., 1993; Sugarbaker, 2007; Glockzin et al., 2009). This phenomenon has prompted further research on the influence of hyperthermia on visceral organs and their nervous supply. Similar therapeutic modalities such as hyperthermic isolated limb perfusion (HILP), pelvic and whole body hyperthermia and radioablation will also be briefly mentioned, as will radiofrequency ablation.

The effect of hyperthermia on the central nervous system (CNS) has been the subject of some research, but the effect on the peripheral autonomic nervous system (ANS) has been less well documented. In this review we will discuss the CNS, peripheral nerves and skeletal muscle as well as the less well-documented subjects of the peripheral ANS and smooth muscles, and how diseases such as MH or heat stroke affect these systems. As is seen in HIPEC and other therapeutic modalities such as whole body hyperthermia and radiofrequency ablation of cardiac muscle, hyperthermia can and does affect end organs directly, and this is the primary focus of this review.

2. The central nervous system and heat stroke

The influence of hyperthermia on the CNS has been investigated, and must be the basis for considering the peripheral nervous system. The symptoms of heat stroke have been thought to be mainly the result of the effect of hyperthermia on the CNS, as the cardinal symptom of exertional heat stroke is confusion leading eventually to coma. White et al. (2007) discussed that humans are particularly vulnerable to temperatures above 40.5 °C; at this temperature the brain's ability to thermoregulate becomes compromised, and irreversible multi-organ dysfunction can occur. Hyperthermia was shown to cause neuronal damage, which especially exacerbates pre-existing conditions, such as ischemia or hypoglycaemia. The extent of this damage depends on both the temperature and duration of exposure. Mechanisms of neuronal injury are controversial; the studies done are in the main on cultured neuronal cells, rather than in-vivo studies, in order to be able to investigate these mechanisms.

Vogel et al. (1997) studied the effects of hyperthermia on survival, DNA degradation, and nuclear morphology of cultured rat cortical and hippocampal neurones. In cultures that were grown for 8 days, heating to 45 °C killed nearly 50% of the cells within 24 h, but only a small portion of the cells died due to apoptosis. At this 24 h mark, the majority of the neurones showed random DNA degradation and were therefore assumed to have died by necrosis. Conversely, after 15 days in culture, hyperthermia resulted in apoptotic morphology in the majority of neurones. The length of time for which the cells were cultured, therefore appears to be an important factor in whether necrosis or apoptosis occurs as a result of heat stress.

Theories about the cause of the hyperthermic damage include endoplasmic reticular stress due to denaturing of polypeptide chains and nuclear and cytoskeletal damage, as mentioned in Vogel et al. (1997). White et al. (2003), used rat embryonic striatal neurones in culture to study mechanisms underlying hyperthermia-induced neuronal death. Heat stress at 43 °C for 2 h produced no obvious signs of damage during the first 12 h after the stress, but more than 50% of the neurones died during the next 3 days. The neurones in White et al.'s study (2003) were cultured for 7–12 days, and therefore, according to Vogel et al. (1997) one would expect some necrosis (as was seen after 8 days) and some apoptosis (as was seen at 15 days of culture). Indeed, slightly more than 40% of the neurones had activated caspases 24 h after the heat stress, consistent with apoptosis. Neuronal death measured 1–3 days after the stress was reduced by using a caspase inhibitor, proving that the caspases are active, and therefore that apoptosis is occurring at 1–3 days. It may have been prudent in this study to use defined and varying length of cultures in order to fully determine whether this effected apoptosis and necrosis. The inhibitor worked even when added 9 h after cessation of the heat stress, consistent with the delayed activation of caspases. This therefore shows that the effect of hyperthermia is not only irreversible, but indeed, neuronal death continues to escalate even after the heat stress had been removed. So, while there are hints to some early mechanisms producing irreversible damage, more research into the major mechanisms is necessary.

2.1. Central autonomic structures

The hypothalamus is the part of the CNS where blood pressure, body temperature, fluid and electrolyte balance, and body weight are held to a precise set-point. The medulla is also a key central nervous system region involved in the ANS. It maintains of basal sympathetic nervous discharge and mediates sympathetic nerve responses from supraspinal sites. In addition to the brain, preganglionic neurones of the sympathetic division of the ANS, which are located in the spinal cord and those of the parasympathetic division, which are located in both the spinal cord and the cranial nerves, can also be affected by heat.

2.1.1. The hypothalamus

There is little research on the direct effects of hyperthermia on the hypothalamus. Studies done on both the hypothalamus and the medulla have been performed using intact animals subjected to whole body or ambient hyperthermia. This poses a difficulty when discussing the mechanism of the effects of hyperthermia, as well as it being unclear whether the observed effects are really due to hyperthermia affecting another body system, or due to localized effects of heat