The pathophysiology of rhabdomyolysis in ungulates and rats: towards the development of a rodent model of capture myopathy

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Contributions

CL, LM, TK, BH, and DWW all contributed to the conceptualisation, writing, and review of the manuscript. All authors also contributed to the review of past and present literature that was considered in this work. All authors read and approved the final manuscript.

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Abstract

Capture myopathy (CM), which is associated with the capture and translocation of wildlife, is a life-threatening condition that causes noteworthy morbidity and mortality in captured animals. Such wildlife deaths have a significant impact on nature conservation efforts and the socio-economic wellbeing of communities reliant on ecotourism. Several strategies are used to minimise the adverse consequences associated with wildlife capture, especially in ungulates, but no successful preventative or curative measures have yet been developed. The primary cause of death in wild animals diagnosed with CM stems from kidney or multiple organ failure as secondary complications to capture-induced rhabdomyolysis. Ergo, the development of accurate and robust model frameworks is vital to improve our understanding of CM. Still, since CM-related complications are borne from biological and behavioural factors that may be unique to wildlife, e.g. skeletal muscle architecture or flighty nature, certain differences between the physiology and stress responses of wildlife and rodents need consideration in such endeavours. Therefore, the purpose of this review is to summarise some of the major etiological and pathological mechanisms of the condition as it is observed in wildlife and what is currently known of CM-like syndromes, i.e. rhabdomyolysis, in laboratory rats. Additionally, we will highlight some key aspects for consideration in the development and application of potential future rodent models.

Keywords: Capture myopathy; Rhabdomyolysis; Exertion; Wildlife; Rat; Animal model

Introduction

Capture myopathy (CM), which manifests in captured wildlife, most notably so ungulates, is a life-threatening condition that causes noteworthy morbidity and mortality (Breed et al. 2019; Spraker 1993; West et al. 2014). Deaths related to capturing of wild animals arise from either metabolic, i.e. CM, or neuropsychiatric, i.e. capture stress (CS), conditions or a combination of both (Meyer et al. 2008a, b). Globally, CM accounts for the highest number of deaths associated with the capture and translocation of wildlife (Breed et al. 2019). However, these procedures are central in efforts to conserve wildlife and biodiversity, and to ensure a sustainable and well-managed ecotourism sector (Breed et al. 2019; Tarszisz et al. 2014). Wildlife deaths due to capture-induced complications have a significant, double-edged impact on nature conservation efforts and the socio-economic wellbeing of communities reliant on ecotourism for an income (Isaacs 2000; Tarszisz et al. 2014) on the one hand, and animal welfare in general, on the other. That said, there is a paucity of data that accurately reflect how many animals die from capture myopathy. While several strategies are used to minimise the adverse consequences associated with wildlife capture, no definitive preventative or curative measures have yet been developed (Dickens et al. 2010; Tarszisz et al. 2014). Apart from sudden death sometimes caused by stress-induced cardiac failure, the primary cause of death in wild animals diagnosed with CM stems from kidney or multiple organ failure that arise as secondary complications to capture-induced rhabdomyolysis (for an in-depth review of the various classifications of capture myopathy, refer to Breed et al. (2019).

To this extent, the development of model frameworks, e.g. a laboratory rodent model, would be of great value to help improve our understanding of capture-induced rhabdomyolysis. The overall usefulness of such models would depend on the accuracy with which they can succeed in mimicking the aetiology and pathophysiology of the clinical condition. However, capture-induced rhabdomyolysis manifests as a result of several converging factors that may be unique to wildlife, e.g. the overall conditions and exertion at capture (Breed et al. 2019; Brown 2015), physiological and tissue changes occurring during capture (Llada et al. 2019; Meyer et al. 2008a, b; Meyer 2010), as well as the specific capture methods and capture drugs used (Breed et al. 2019; Businga et al. 2007; Harthoorn et al. 1974; Smith et al. 2005) and the related stress responses they cause (Breed et al. 2019; DeNicola and Swihart 1997; Sheriff et al. 2011). Translational rodent models have realised varied levels of success in emulating the bio-behavioural and treatment response characteristics of human stress-related conditions and are used to identify novel drug targets as well as testing new pharmacotherapies for these disorders (Bouwknecht 2015; Demin et al. 2019). Such an approach should be explored in wildlife research as well, although there are few such models available for veterinary application. Thus, toward the development of a successful rodent model of capture-induced rhabdomyolysis, a thorough understanding of how wildlife and rodents may differ with respect to the underlying architectural components of rhabdomyolysis, would be valuable. Since rhabdomyolysis itself has been reviewed extensively elsewhere (Bartsch et al. 1977; Blumstein et al. 2015; Breed et al. 2019), the purpose of this review will be to summarise some of the major pathophysiological mechanisms of the condition as it is observed in wildlife and what we currently know of rhabdomyolysis in laboratory rats. Additionally, we will highlight some key aspects for consideration in the development and application of potential future rodent models.

Rhabdomyolysis – background and pathophysiological summary

Capture related rhabdomyolysis in wildlife

Aetiology

Rhabdomyolysis associated with CM is a metabolic muscle condition that arises in some recently captured wild animals (Breed et al. 2019; Khan 2009). Stress, exertion, and crush injury are well-documented causes of rhabdomyolysis, but other causes, e.g. procedures that involve long periods of restraint, struggling from unnatural positioning, or lengthy pursuit intervals during capture, also contribute to the development of rhabdomyolysis in wildlife (Blumstein et al. 2015; Bartsch et al. 1977; Breed et al. 2019; Williams and Tucker 1983). Since captured animals often also present with an increase in cellular oxygen consumption, which results from both flight- and drug-induced sympathetic nervous system activation and hypermetabolism, this may result in vasoconstriction, hyperthermia and often thus hypoxia which can be exacerbated by drug-induced respiratory compromise (Buss et al. 2018; Meyer et al. 2008a, b) and contribute to the aetiology of the condition. In this way, immobilising drugs may also contribute to and result in pathophysiological trauma and contribute to rhabdomyolytic damage (Lance 2013; Meyer et al. 2008a, b; Spraker 1993). Under such circumstances, oxygen supply and cellular energy production fails to match the oxygen and metabolic demand, disrupting cell function and integrity, possibly leading to organ damage and rhabdomyolysis (Meyer et al. 2008a, b). This is problematic, since chemical immobilisation during capture procedures, can, in some circumstances, not be avoided. Importantly, the effects of immobilising drugs on thermoregulation may vary depending on the pharmacological profile. For example, opioids, e.g. thiafentanil and etorphine, alpha-2 (α_2) agonists, e.g. medetomidine and xylazine, butyrophenones, e.g. azaperone and haloperidol, benzodiazepines, e.g. diazepam and midazolam, and cyclohexanones, e.g. ketamine (Cooper et al. 2005; Meyer et al. 2008a, b; Zeiler and Meyer 2017), are known to alter the thermoregulatory processes of animals and may play a role in CM and capture-induced hyperthermia (Fahlman et al. 2008). Further, opioids may also contribute to muscle rigidity which ranges from occasional myoclonic contractions to generalised full body muscle rigidity and catalepsy (Breed et al. 2019; Khan 2009; Wolfe and Miller 2016). Collectively, these findings highlight a need for novel therapeutic interventions with an improved safety profile, as well as a better understanding and use of capture drugs.

Pathophysiology

Rhabdomyolysis is primarily characterised by muscle necrosis and myoglobinuria (Bagley et al. 2007; Breed et al. 2019; Khan 2009) and manifests when the inherent biological stress defences of an animal fail or are in the process of failing (Blumstein et al. 2015). The rhabdomyolytic process normally results in a surge of cytoplasmic components, which occurs mostly due to muscle breakdown or injury to muscle fibres. Said components include myoglobin, creatine kinase (CK), and lactate that enter the systemic circulation after being released from muscle fibres (Meyer et al. 2008a, b; Spraker 1993; Vanholder et al. 2000). Clinically, animals present with a combination of clinical signs ranging from lethargy, muscular stiffness, muscle fibrillation, tachypnoea, tachycardia, weakness, incoordination, recumbency, partial paralysis, hyperthermia (often manifesting as core temperatures higher than 42 °C), metabolic acidosis and myoglobinuria (Bartsch et al. 1977; Breed et al. 2019; Harthoorn 1976; Meyer et al. 2008a, b). On gross examination, muscle necrosis, dark, red-stained renal medullae, and dark-coloured urine (Breed et al. 2019; Harthoorn 1976; Llada et

al. 2019) are seen. The condition carries a poor prognosis, and despite rigorous prolonged and largely non-specific supportive treatment, the recovery rate is poor (Meyer et al. 2008a, b; Meyer 2010). Death usually follows within six hours after capture due to acute renal or cardiac failure (Guis et al. 2005), respiratory distress, liquid volume and electrolyte depletion, metabolic acidosis, azotaemia and/or disseminated intravascular coagulation, but can also occur weeks later due to chronic renal and/or cardiac failure (Bartsch et al. 1977; Breed et al. 2019; Chalmers and Barrett 1977; Khan 2009).

In extension to the pathophysiological mechanisms that underlie CM which have been alluded to above, CS is also contributory. Capture stress is an intense neuropsychiatric stress condition which involves an exacerbated state of arousal during capture attempts (Knox et al. 1990; Meltzer and Kock 2006). However, as animals are unable to escape the perceived danger—in this case being captured—uninhibited arousal leads to a persistent state of anxiety that is associated with excessive sympathetic nervous system activation. Indeed, the major neural response to acute capture CS is a generalized and immediate activation of the fight-or-flight response, as an animal in this state decides almost instantly whether to defend or run (Stratakis and Chrousos 1995; Fowler and Miller 2008). Once triggered via the central nervous system (CNS), initial activation of the sympathetic nervous system subsequently incites the release of catecholamines (adrenaline and noradrenaline) from the adrenal medulla (Paterson 2007), which, while resulting in an immediate increase in ATP availability, causes rapid depletion of ATP stores as time progress (Meyer 2010). This, in combination with sympathetic system hyperactivation, can contribute to the pathophysiology of rhabdomyolysis in a significant way, as will be discussed later in this review.

The variability in prognosis seen with capture-related complications, can likely be ascribed to the fact that four distinct clinical syndromes, i.e. capture shock syndrome, ruptured muscle syndrome, ataxic myoglobinuric syndrome and delayed peracute syndrome, may arise to varying degrees in captured ungulates (Herráez et al. 2007; Spraker 1993). Animals with capture shock syndrome tend to die within 1 – 6 h and mainly present with tachypnoea, tachycardia, a weak pulse, hyperthermia, and lethargy before death (West et al. 2014). Macroscopic lesions include intestinal, hepatic, and pulmonary congestion, while elevated lactate dehydrogenase (LDH), CK and aspartate aminotransferase (AST) activity (Spraker 1993) occur in combination with metabolic acidosis (Harthoorn 1976). Animals suffering from ruptured muscle syndrome appear normal at first, with clinical signs appearing 1 to 2 days after capturing. Death usually follows within a few days, but some animals may survive for a few weeks (Spraker 1993). As its name suggests, ruptured muscle syndrome is mostly associated with ruptured gastrocnemius muscles that result in dropped hindquarters and hyperflexion of the hocks (Spraker 1993). Often, these animals are unable to stand, giving rise to tetraplegia. Torticollis is also often evident because of cervical muscle injury (Harthoorn 1976). Animals presenting with the ataxic and acute myoglobinuric syndromes show varying degrees of ataxia, torticollis and myoglobinuria. Pathological findings include mild to moderate rhabdomyolysis affecting the cardiac and skeletal muscle with elevations in serum LDH, CK and AST, as well as blood urea concentrations (Bartsch et al. 1977; Harthoorn 1973; Spraker 1993). Furthermore, renal lesions have been described. These are characterised by tubular necrosis with intra-tubular protein casts, while the urinary bladder usually contains a small amount of brownish urine (Herráez et al. 2007; Spraker 1993). Death follows within hours to a few days after the capture event, but animals presenting with mild symptoms may have a greater chance of survival (Breed et al. 2019; Harthoorn 1976). It is evident that rhabdomyolysis plays a central role in the pathological presentation and outcome of CM as described in various clinical syndromes.

Rhabdomyolysis in laboratory rodents

Aetiology

Several rodent models have been developed to mimic clinical acute rhabdomyolysis-induced renal failure and to understand the mechanisms underlying such renal injury (Nath et al. 1992; Reis et al. 2019; Soares et al. 2002). Genetically modified rodent strains, which mimic specific congenital myopathies that result in rhabdomyolysis and renal injury from acute exercise, are widely used to better understand myopathy conditions in humans. These conditions include metabolic myopathies, e.g. McArdle's disease (Almodóvar-Payá et al. 2020), muscle structural abnormalities (which occur in dystrophic animal models) (Gaina 2021), and organelle specific abnormalities, such as perturbations in the calcium-binding protein calsequestrin (Woo et al. 2020), located in the sarcoplasmic reticulum.

Rhabdomyolysis can also be induced by the intramuscular administration of certain chemicals. Glycerol is commonly used to induce and investigate rhabdomyolysis-related renal injury. This model is characterised by myoglobinuria, tubular necrosis (Karam et al. 1995; Singh et al. 2012) and increased renal vasoconstriction (Singh et al. 2012). Renal failure is induced by the intramuscular administration of 50% (v/v) glycerol into both hind legs of rats (Singh et al. 2004, 2012; Zurovsky 1993). The pathogenic mechanisms involved in glycerol-induced renal failure include ischemic injury, tubular nephrotoxicity caused by myoglobin, and pathological damage caused by cytokines released during the rhabdomyolytic process (Curry et al. 1989; Khan 2009; Singh et al. 2012). Rats injected with intramuscular glycerol also present with elevated concentrations of blood urea and creatinine as well as depleted glutathione concentrations (Singh et al. 2004, 2012; Zurovsky 1993). Kidneys present with moderate epithelial necrosis, tubular dilation, and myoglobin-derived haem casts (Tsai et al. 2017).

Strenuous forced treadmill running can also induce rhabdomyolysis and concomitant renal injury in healthy rats (Chen et al. 2013; Gündüz and Şentürk 2003). Although not focused on studying rhabdomyolysis per se, this research applies strenuous exercise protocols to better understand the role of exercise intensity and duration on muscular anatomy and physiology. Furthermore, the influence of different pathophysiological states, such as exacerbated oxidative stress on muscle function and muscular damage, can be investigated using this rat model (Amelink and Bär 1986; Liu et al. 2000; Michelucci et al. 2017). Forced running-induced pathology includes mild to moderate damage affecting both cardiac and skeletal muscle (Oláh et al. 2015) that are associated with increased plasma CK, AST, and LDH concentrations in animals of both sexes immediately after exercise (Armstrong et al. 1983; Komulainen et al. 1995; Oláh et al. 2015; Van der Meulen et al. 1991). Apart from the induction of rhabdomyolysis in this model, forced running can also induce both psychological and physical stress. Indeed, forced exercise regimens usually include aversive motivation which may lead to anxiety and activate the stress response (Brown et al. 2007; Leasure and Jones 2008). Thus, in light of both the rhabdomyolytic and stress components observed in the forced running rat model, and considering that both of these constructs are recognised prodromal factors in captured animals that develop CM, it may be a valuable model to study capture myopathy (Moraska et al. 2000; Svensson et al. 2016).

Pathophysiology

Glycerol-induced rhabdomyolysis in rats invariably results in muscle necrosis, myoglobinuria and subsequent acute renal injury. On gross examination, cortical and renal tubular lesions are

present (Reis et al. 2019). As in wildlife, precipitated myoglobin in the distal tubules eventually leads to tubular destruction (Breed et al. 2019; Spraker 1993). These rats have been shown to present with higher fractional sodium excretion, increased plasma creatinine and CK, and a decreased glomerular filtration rate (GFR) (Nath et al. 1992; Reis et al. 2019; Soares et al. 2002). Furthermore, myoglobin-associated renal injury causes similar secondary pathophysiological effects as those observed in wildlife, which are characterised by increased levels of oxidative stress, inflammation, endothelial dysfunction, splanchnic vasoconstriction and glomerular cell apoptosis (Panizo et al. 2015; Reis et al. 2019).

With respect to strenuous exercise-induced rhabdomyolysis, rats present with increased markers of oxidative stress. Although significant increases in free radical production is a normal occurrence during exercise, excessive free radical production could have a detrimental effect on both cardiac and skeletal muscle function and integrity, and leads to increased plasma CK, AST and LDH concentrations (Armstrong et al. 1983; Komulainen et al. 1995; Oláh et al. 2015; Powers et al. 1999; Van der Meulen et al. 1991).

In general, the prognosis associated with rhabdomyolysis in rats varies, likely because of differences in causation. The prognosis of glycerol-induced rhabdomyolysis is poor due to permanent kidney damage and poor renal function (Nath et al. 1992). On the other hand, CM induced by forced exercise regimes is associated with variable outcomes and prognosis, which can likely be ascribed to the different severities of muscle damage induced by the varying exercise intensities (Chen et al. 2013; Liu et al. 2000).

From field to bench – translational aspects for consideration

As alluded earlier in this review, CM-associated rhabdomyolysis in wild animals is a diverse condition that varies in terms of manifestation and pathophysiology (Breed et al. 2019). While the glycerol-induced and strenuous exercise-induced rodent models reviewed above may emulate some aspects of rhabdomyolysis in wild animals, no truly wildtype rodent model system has yet been validated to study the pathophysiological mechanisms underlying capture-induced and stress-related rhabdomyolytic pathology. Such a model should ideally present the naturalistic progression from health to CM that typifies the condition and that cannot be predicted in the field. These models would therefore also be helpful to expand our understanding of the underlying biology of the condition as well as to explore, identify and formulate appropriate intervention strategies. However, for a rodent CM model to be established, two primary constructs of CM arguably need to be considered, i.e. an inflated flight response accompanied by increased sympathetic nervous and adrenal system function, and increased muscular activity, which interacts with the former in a way that leads to rhabdomyolysis (Breed et al. 2019; Paterson 2007; Vanholder et al. 2000). Since rodents may differ significantly with respect to these constructs, we will summarise some key aspects for consideration.

An inflated flight response

Capture-induced stress appears to be one of the key precipitating factors of CM (La Grange et al. 2010). Ungulates are naturally anxious and flighty, a characteristic that tends to contribute towards the high rates of mortality and morbidity in captured wildlife (Knox et al. 1990, Blumstein et al. 2015; Breed et al. 2019). Importantly, some species are more stress-prone than others, e.g. certain antelope like tsessebe *(Damaliscus lunatus lunatus)*, compared to blue wildebeest *(Connochaetes taurinus)* (Breed et al. 2019). Indeed, capture-induced stress is

believed to be an intense neurobiological stress condition, which involves an exacerbated state of arousal, among others (Hattingh et al. 1992; Knox et al. 1990; Meltzer and Kock 2006). Nevertheless, as animals are unable to escape the perceived danger—in this case being captured—uninhibited arousal leads to a persistent state of fear-anxiety that is associated with excessive sympathetic nervous system activation which may result in the pathophysiology which causes rhabdomyolysis (Meltzer and Kock 2006), as earlier alluded in this work.

The major neural response pattern to acute capture-induced stress involves a generalised and immediate activation of the fight-or-flight response, as animals in this state decide almost instantly whether to defend themselves or flee (Bonne et al. 2004; Fowler and Miller 2008). Human presence, high speed chasing by motorised vehicles, abnormal smells and sounds during capture, separation from the larger group, and restraint after capture, cause a noteworthy degree of anxiety and distress in captured wildlife (Breed et al. 2019; Spraker 1993; Wolfe and Miller 2016). Most of these factors can be applied to some extent as fear-inducing stimuli in rodent models (Buynitsky and Mostofsky 2009; Ganella and Kim 2014; Wang et al. 2020).

Rodent stress models are widely used to examine the biobehavioural mechanisms that may underlie human stress disorders, as noted earlier. Although some components of capture-induced stress are varyingly mimicked in preclinical work, it is mostly true that the majority of stress paradigms used in the laboratory bear little resemblance to the natural conditions prevailing in the wild. For example, while maternal separation (Wang et al. 2020), electric foot shock (León et al. 2017), restraint (Brand and Harvey 2017), and inescapable forced swim stress (du Jardin et al. 2016) are commonly used to induce stress in the laboratory, these techniques do not accurately resemble the above-mentioned conditions which wild animals normally face during capture. Rodents may be affected in a unique way during such procedures, in that the full extent and time-related (i.e. during different phases of the capture process) of the various stressors experienced by captured wildlife cannot be replicated in a manner that is ethologically appropriate to laboratory rats. That said, it must be stated that for wildlife, capturing elicits a form of severe stress that does not resemble the 'normal' everyday challenges and fear responses that wild animals may experience. For example, in the wild, antelope would not readily develop rhabdomyolysis when surprised and chased by predators, since such chases are normally of short duration. Also, predation is a natural phenomenon, which in the absence of added unnatural stressors, e.g. human presence, would likely elicit a tolerable degree of stress (Bartsch et al. 1977). However, when captured, wild animals are often forced to run at high speeds for longer distances while being chased by motorised vehicles (Brown 2015; Breed et al. 2019). Such 'unnatural' interference during capture procedures arguably provides preclinical research with a conceptual advantage, since it would be possible to induce a similar 'unnatural' stress response in laboratory rodents, without the need to accurately reproduce the exact conditions of wildlife capture in the field.

To this extent, an appropriate model of CM in rodents could be based on forced treadmill running, which can mimic the physical intensity of wildlife chases. In fact, the metabolic demands of running at high intensity, i.e. at 70 – 90% of maximal O_2 consumption (VO_2 max; Schoeman et al. (2017)), are known to produce neural and endocrine responses which are indicative of acute physical stress (Brooks et al. 1996; Moraska et al. 2000), e.g. increased corticosterone secretion, a clinical marker of an activated psychobiological stress response (Brown et al. 2007). In addition to mimicking the physical exertion induced by being chased, forced treadmill running would arguably also produce a neurobiological stress response similar to that experienced by wildlife (Brooks et al. 1996; Moraska et al. 2000).

As Spraker (1993) describes, fear and exhaustion can both result in excessive activation of the sympathetic nervous system which is characterised by the increased release of catecholamines and corticosteroids. In turn, this will result in increased arterial pressure, accelerated cellular metabolism, hyperglycaemia, increased blood coagulation and glycogenolysis (Spraker 1993). Elevated catecholamine release can also cause renal vasospasm, in turn increasing serum urea and creatinine concentrations (Mentaberre et al. 2010). Collectively, adrenergic hyperactivation, though predominantly recruited to ensure fight or flight readiness, may be detrimental to the animal over the longer term. In fact, it contributes to adenosine triphosphate (ATP) depletion in muscle cells, reduced blood oxygen delivery to target tissues, hypoxaemia, lactic acid accumulation as well as a reduced removal rate of metabolic by-products from muscle cells (Paterson 2007). Ultimately, this will result in muscular injury and necrosis (Blumstein et al. 2015). Against this background, forced treadmill running may be a suitable model system in which these and other pathophysiological mechanisms that may underlie CM, can be investigated.

Heightened muscular activity and rhabdomyolysis

Skeletal muscle architecture

A second core construct of CM in wild animals is muscle damage which results from physical exertion and/or stress-induced muscle degeneration after the capture procedure (Harthoorn 1976; Spraker 1993). The primary muscles affected are the quadriceps, gastrocnemius, cervical and lumbar muscles, where severe muscle necrosis is presented—a classic sign of CM. Considering the vast divide between the anatomical frame and musculoskeletal mechanics in wildlife and rats, translational studies into the manifestation and aetiology of capture-induced rhabdomyolysis, would likely be challenging. The locomotor muscles of large mammals (including humans) are primarily composed of three fibre types, namely types I, IIA and IIX (Kohn et al. 2011; Rivero et al. 2007; Smerdu et al. 2009). The physical characteristics of these fibres are derived from the type of myosin heavy chain (MHC) isoform each expresses. MHC I is characteristic of fibres that have a slow contraction speed but are normally rich in myoglobin and mitochondrial content, making them highly fatigue resistant. MHC IIA expressing fibres are slightly slower in contraction speed than type IIX fibres. They contain a larger number of mitochondria and produce ATP by means of both aerobic and anaerobic metabolism, rendering these fibre types to be moderately resistant to fatigue (Kohn and Myburgh 2007). Fibres expressing MHC IIX display the fastest contraction speed of the three types but normally have low myoglobin concentrations and lower mitochondrial numbers. These fibres also have a poor oxidative, but high anaerobic capacity, compared to type I and IIA fibres. As a result, these fibres are prone to fatigue rapidly, while they generate high concentrations of lactate and other metabolic breakdown products resulting from anaerobic processes. That said, in the wild, these fibres are recruited mostly during short-distance flight sequences and hence contribute little to the normal ambulatory activity of animals.

Muscle recruitment, energy turnover and metabolic profile

It stands to reason that the recruitment of various combinations of fibre types will provide varying performance and endurance capacities to a specific muscle group. Importantly, skeletal muscles of the wild antelope of Southern Africa, as highlighted above, do not conform to the fibre type classification and metabolic profiles found in laboratory rats. In fact, rat muscle expresses four MHC isoforms (Hohl et al. 2020). Specifically, rats also express MHC IIB, which have high myosin ATPase activity, are fast twitch, have low oxidative and high

glycolytic capacity, and fatigue rapidly. Only trace amounts of this protein have been described in cheetah *(Acinonyx jubatus)*, llama *(Lama glama)*, and pig *(Sus domesticus)* limb muscles (Graziotti et al. 2001; Hyatt et al. 2010; Kohn and Myburgh 2007; Toniolo et al. 2004), while most of the larger mammalian species express MHC IIB in smaller, specialised fibres, e.g. the intra- and periocular muscles (Toniolo et al. 2004). From a translational perspective, this difference might be problematic, since the fibre types that are recruited by rats and wildlife during 'flight' responses might result in distinct pathophysiologial profiles on three levels (Hohl et al. 2020), that is ATP turnover, reactive oxygen species (ROS) generation, and gross pathological presentation.

In terms of ATP, it was shown that the muscle of antelope, and not that of rats, has an inherently high capacity to generate ATP, which in turn predicts a high rate of ROS production (Hohl et al. 2020); however, antioxidant enzyme activity appears to be similar or only slightly higher than that found in the rat locomotor muscles (discussed later) (Hohl et al. 2020). Given the overall low oxidative capacity of especially the fast-twitch type IIX fibres, the question remains whether ATP supply from muscle glycogen can match ATP demand during high-speed, extended capture procedures. The answer to this question is important, since depletion of ATP in myocytes triggers an increase in intracellular calcium that leads to persistent contraction of the muscle fibres (in essence, rigor) (Breed et al. 2019). Furthermore, considering the physical impact of capture procedures on wildlife, ATP depletion can be exacerbated by sarcolemma injury. This effect not only culminates in membrane damage and muscle fibre necrosis, but also causes the release of their intracellular contents, e.g. phosphorus, potassium, myoglobin, CK, AST, LDH, urates, purines and inflammatory cytokines into the extracellular space and the systemic circulation (Breed et al. 2019). These effects, which can transpire because of physical exertion, are exacerbated by the simultaneous activation of the stress cascade. In stressed animals, β_2-adrenergic receptor stimulation results in an increased production of cyclic AMP, which accelerates glycogenolysis and glycolysis, contributing to a further increase in ATP synthesis (Levy 2006) and energy turnover. Since rodents and wildlife likely recruit different muscle fibres under circumstances of physical exertion, preclinical, forced-running induced models of CM might involve different ATP-specific mechanisms underlying the manner in which myofiber damage is induced.

In extension, ATP generation is linked with the production of ROS and reactive nitrogen species (RNS). This is not only problematic given the differences in the oxidative capacity between some muscle groups, but also because excessive ROS are known to impair mitochondrial oxidative phosphorylation, leading to heat production and triggering rhabdomyolytic cell death (Busiello et al. 2015; Powers et al. 2016). In this regard, type IIX skeletal muscle fibres are unique in that they are especially prone to generate high ROS concentrations (Hohl et al. 2020). This construct also needs consideration in the development of rodent models of CM, since translational conclusions regarding the relationship between muscle phenotype and oxidative capacity using laboratory animals should be drawn with caution. For example, apart from pointing to the fact that antelope may be subjected to a higher degree of oxidative stress during high-intensity running episodes, Hohl et al. (2020) further suggest that mitochondrial numbers and aerobic capacity are not necessarily determined by fibre type in wild species. Black wildebeest *(Connochaetes gnou)*, for instance, having some of the highest type I and IIA fibre proportions, show a mitochondrial capacity akin to that of other wild antelope species. Additionally, and as previously alluded, antelope also harbour oxidative type IIX fibres, which has also been described in dogs and reindeer *(Rangifer tarandus)*, black wildebeest, springbok *(Antidorcas marsupialis)*, blesbok *(Damaliscus pygargus phillipsi)*, fallow deer *(Dama dama)*, mountain reedbuck *(Redunca fulvorufula)* and

kudu *(Tragelaphus strepsiceros)* (Acevedo and Rivero 2006; Curry et al. 2012; Essén-Gustavsson and Rehbinder 1985; Kohn et al. 2011; Kohn 2014). Thus, it appears that while antelope may produce relatively high levels of ROS during stressful and exerting situations, they might present with sufficient antioxidant mechanisms. In contrast, rodents seem to conform to the classic understanding that total oxidative enzyme capacity correlates with the percentages of type I and/or type IIA fibres, depending on the training state of the animal (Chi et al. 1986; Delp and Duan 1996; Kohn and Myburgh 2007) and thus the exact relationship between ROS generation and CM in rodents might be different from that found in wildlife.

Moreover, several differences between the antioxidant systems in wildlife and rats also need highlighting. In general, the major mammalian antioxidant enzymes are superoxide dismutase (SOD), catalase (CAT) and the glutathione peroxidase (GPX)/glutathione reductase (GR) systems (Powers et al. 1999). However, Hohl et al. (2020) have shown that wild antelope express a greater degree of SOD activity, compared to rats. Further, whereas rodents show high CAT activity in the left ventricle and deep gastrocnemius muscle—known to have high anaerobic capacity and mitochondrial number—CAT in wild animals is more prominent in the less oxidative muscles (Hohl et al. 2020). Interestingly, this contrasting pattern is also shown for CK activity, in that rats express a five-fold higher CK activity in the white gastrocnemius muscle compared to wild animals (Hohl et al. 2020). Creatine kinase has pro-oxidant activity since it is an important role player in the rapid re-synthesis of ATP, which ultimately lead to ROS generation (Hohl et al. 2020). Specifically, CK forms the core component in phosphocreatine (PCr) energy circuit (Saks 2008), where mitochondrial CK (MtCK) recruits mitochondrial ATP to regenerate cytosolic PCr. This shuttle system is vital for the production and maintenance of the energy supply, while it also plays a role in the regulation of cellular respiration (Saks 2008). It is therefore not surprising that skeletal muscle expresses high levels of CK which catalyses the reversible phosphorylation of creatine to PCr and of ADP to ATP (Brancaccio et al. 2007; Sayers and Clarkson 2003). The fact that Hohl et al. (2020) demonstrated a lower CK but a higher SOD activity in wild antelope could point to a protective antioxidant effect in wildlife, which may not be as effective in rats, especially since, unlike in rats, CK and SOD activity in wildlife are independent from fibre type content or oxidative capacity (Hohl et al. 2020). These findings are important for the development of future rodent models of CM and highlights the importance of investigating different muscle fibres from both sedentary and trained rodents, and where possible from wildlife animals, to improve our understanding of the role of ROS generation and antioxidant activity in the development of CM.

Gross pathological presentation

On macro-pathological examination, muscle necrosis, dark, red-stained renal medullae and dark-coloured urine are observed in wild animals that develop rhabdomyolysis (Harthoorn et al. 1974).

Generally, the appearance of affected muscles varies with time after onset; however, multifocal haemorrhage and necrosis have been the main macroscopic lesions (Bartsch et al. 1977). Damaged muscles often have multifocal pale, soft, dry areas that are accentuated by small white foci in a linear pattern which are usually found within the cervical and lumbar muscles and in the flexor and extensor muscles of the limbs (Spraker 1993). In this regard, the distribution of muscle lesions varies considerably, with commonly ruptured muscles being the gastrocnemius, subscapularis, middle and deep gluteal, semitendinosus and the semimembranosus muscles (Spraker 1993). Lesions are usually bilateral, but not necessarily

symmetrical and are subtle in animals that die within one to two days after capture; they are however more pronounced in animals that survive longer (Spraker 1993). In antelope, the most severe lesions are found in muscles of the pectoral girdle and flexors of the hips (Bartsch et al. 1977). Also, acute renal injury, which is characterised by a rapid decline of the GFR, is a severe consequence of the condition (Guis et al. 2005).

Although the exact pathogenesis of rhabdomyolysis-induced acute renal injury is poorly understood, myoglobin-induced renal toxicity plays a key role. This is caused via three myoglobin-induced mechanisms, i.e. (i) excessive vasoconstriction, (ii) intraluminal cast formation and (iii) heme–protein-induced cytotoxicity (Vanholder et al. 2000). Furthermore, a prolonged state of splanchnic vasoconstriction during the fight-or-flight phase of the stress response may induce renal ischaemia, exacerbating the pathological effects of myoglobin. Such hypoxic damage to the glomeruli can contribute to proteinuria that in turn can cause renal tubule obstruction and a reduction in the glomerular filtration rate (Vanholder et al. 2000). While myoglobin is usually filtered by the glomerular basement membrane, metabolic acidosis caused by physical exertion is a driver for myoglobin precipitation and cast formation. Also, ferrihemate, a metabolic breakdown product of myoglobin, has direct nephrotoxic effects by catalysing free radical production, lipid peroxidation, in turn resulting in oxidative cell injury (Spraker 1993; Vanholder et al. 2000). These findings have been somewhat corroborated in rodent models (Liu et al. 2000), but only by means of glycerol-induced injection and not due to physical exercise. Whether similar pathologies can be induced in exertion-based rodent models remains to be elucidated.

Conclusion

As has been evident throughout the paper, capture-induced rhabdomyolysis (capture myopathy) in wildlife is a condition with a complex cause and pathophysiological presentation (see also Breed et al. (2019) for review), that responds poorly to currently available therapeutic interventions. To this extent, preclinical work in rodent models may be useful to investigate the pathophysiological mechanisms underlying this condition. Considering the noteworthy differences between the nature and physiology of wildlife and rodents, we aimed to briefly review the existing literature on rhabdomyolysis as it manifests in wildlife and laboratory rodents. While the condition is characterised by severe muscle breakdown, renal failure, and elevated body temperatures in both wildlife and rodents, some important differences between wildlife and rodents were highlighted (refer to Table 1 for a summary). Throughout this work, we also highlighted several areas that need consideration in the development of rodent models and we stress that for rodent models to be successful in broadening our understanding of CM, they need to closely emulate the biological, pathological and psychological characteristics of rhabdomyolysis in wild animals.

Table 1 Summary of differences between wildlife and rodents regarding capture myopathy and rhabdomyolytic biobehavioural constructs

Parameter/Construct	Wildlife	Rat
Species / Models	• Mostly shown for antelope, e.g. impala and blesbok, but may also occur in other species	• Sprague–Dawley; • Wistar rats; • Cy/ + rats
Aetiology	• Metabolic disease resulting from stress, exertion, and crush injury; • Can also be due to restraint or lengthy pursuit intervals during capture; • Chemical immobilisation (controversial)	• Intramuscular glycerol administration; • Forced running or swimming; • Genetic modification with exercise (e.g. swimming)
Pathophysiology	• Muscle necrosis; • Myoglobinuria; • Dark, red-stained renal medullae; • Dark-coloured urine; • Acute renal injury; • Significant variability in prognosis	• Muscle necrosis; • Myoglobinuria; • Tubular and renal epithelium necrosis and nephrotoxicity; • Tubular dilation; • Ischemic renal injury; • Myoglobin-derived haem casts
Blood plasma components	• Elevations in plasma: ◦ Myoglobin; ◦ CK; ◦ LDH; ◦ AST; ◦ Urea; ◦ Creatinine; ◦ Lactate, and ◦ H^+	• Elevations in plasma: ◦ CK; ◦ LDH; ◦ AST; ◦ Urea; ◦ Creatinine • Reduction in plasma: ◦ Glutathione
Clinical presentation	• Lethargy; • Muscular stiffness; • Muscle fibrillation; • Tachypnoea; • Tachycardia; • Weakness and incoordination; • Recumbence; • Partial paralysis; • Hyperthermia (usually manifesting as core temperatures higher than 42 °C); • Metabolic acidosis • Death usually within 6 h after capture	• Hyperthermia; • Muscular damage; • Oxidative stress; • Inflammation • Endothelial dysfunction; • Splanchnic vasoconstriction; • Glomerular apoptosis
Muscle and fibre types involved	• Skeletal muscle; mainly ◦ quadriceps; ◦ gastrocnemius; ◦ cervical; ◦ lumbar; • Cardiac muscle; • Three main fibre types: ◦ I; ◦ IIA; ◦ IIX	• Skeletal muscle; mainly gastrocnemius; • Cardiac muscle; mainly left ventricular; • Four main fibre types: ◦ I ◦ IIA ◦ IIX; ◦ IIB
General notes regarding ATP generation	• Inherently high capacity to generate ATP; • ATP generation predicts ROS production; • CK and SOD activity independent from fibre type or fibre content	• Lower inherent capacity to generate ATP; • Oxidative enzyme capacity correlates with the abundance of type I and/or type IIA fibres and training condition of animals

CK: creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ATP: adenosine triphosphate; ROS: reactive oxygen species; SOD: superoxide dismutase

Key factors for consideration:

• Muscle necrosis and myoglobinuria play important roles in CM. It would be of vital importance to investigate which muscles are affected in rodents compared to wildlife

• Considering that certain metabolites, e.g. CK, can also originate from cardiac muscle, careful scrutiny is needed. Since increased CK concentrations may also point to cardiac pathology unrelated CM, it may not serve as a specific marker of CM

• Muscle fibre types of rats and wildlife differ slightly, with rodents having an extra muscle fibre namely IIB. A rodent model of capture myopathy that can provide insight into the contributory effect of different fibre types to the development of muscle necrosis and myoglobinuria, would be valuable

• In wildlife, CM involves four distinct syndromes, either affecting the heart, kidney or skeletal muscle. These four syndromes should be investigated in depth in rodent models. Interestingly, it seems that rodents are especially suited for the study of renal mechanisms, although more work is needed to shed light on more of other pathophysiological constructs seen in wildlife

Data availability

Not applicable.

Ethics approval

No approval of research ethics committees was required to accomplish the goals of this study because this work is a systematic review of published literature.

Consent to publish

Not applicable.

Competing Interests

The authors declare that there is no conflict of interest.

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