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Ketogenic diets and the nervous system: a scoping review of neurological outcomes from nutritional ketosis in animal studies

Rowena Field[1]* , Tara Field[2], Fereshteh Pourkazemi[1] and Kieron Rooney[1]
[1]*The University of Sydney, Faculty of Medicine and Health, Sydney, Australia*
[2]*The New South Wales Ministry of Health (NSW Health), Sydney, Australia*

Abstract

Objectives: Ketogenic diets have reported efficacy for neurological dysfunctions; however, there are limited published human clinical trials elucidating the mechanisms by which nutritional ketosis produces therapeutic effects. The purpose of this present study was to investigate animal models that report variations in nervous system function by changing from a standard animal diet to a ketogenic diet, synthesise these into broad themes, and compare these with mechanisms reported as targets in pain neuroscience to inform human chronic pain trials.

Methods: An electronic search of seven databases was conducted in July 2020. Two independent reviewers screened studies for eligibility, and descriptive outcomes relating to nervous system function were extracted for a thematic analysis, then synthesised into broad themes.

Results: In total, 170 studies from eighteen different disease models were identified and grouped into fourteen broad themes: alterations in cellular energetics and metabolism, biochemical, cortical excitability, epigenetic regulation, mitochondrial function, neuroinflammation, neuroplasticity, neuroprotection, neurotransmitter function, nociception, redox balance, signalling pathways, synaptic transmission and vascular supply.

Discussion: The mechanisms presented centred around the reduction of inflammation and oxidative stress as well as a reduction in nervous system excitability. Given the multiple potential mechanisms presented, it is likely that many of these are involved synergistically and undergo adaptive processes within the human body, and controlled animal models that limit the investigation to a particular pathway in isolation may reach differing conclusions. Attention is required when translating this information to human chronic pain populations owing to the limitations outlined from the animal research.

Keywords: **Ketogenic diet: Animal: Neurological: Beta-hydroxybutyrate: Inflammation**

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Introduction

Nutrition is directly responsible for the delivery of energy for cellular metabolism, as well as providing the diverse array of substrates required for normal physiological function. It also plays a central role in the modulation of inflammatory and disease processes[1–3] and, thus, can be utilised as a therapeutic intervention. Nutritional therapies that limit substrate availability and produce ketosis (such as fasting, calorie restriction and ketogenic diets) directly impact metabolism and cellular energetics[2,4]. Ketosis has been reported to be effective in neurological conditions characterised by neurodegeneration[5–9], psychological disorders[10], brain injury[6,11] and nervous system excitability[12–15]. More recently, the presence of ketones has been suggested to influence pain mechanisms[16–18]. Given this, ketosis produced through a ketogenic diet may be an appropriate treatment strategy for persistent pain, a dysfunction within the nervous system involving changes in both cortical structure and function[19,20]. Neuroplastic remodelling facilitates increased connectivity and amplification of pain perception and is required to shift into a persistent pain state[21]. Broadly, nutritional interventions have been shown to improve pain outcomes[22–24]. Directly targeting neurobiology through a ketogenic diet could potentially modulate maladaptive change and become an additional strategy to add to comprehensive chronic pain management[25].

The concept of nutritional neurobiology for chronic pain management is starting to appear in the literature, where dietary intake can be both a trigger for upregulated pain mechanisms but also potentially provide therapeutic options[25,26]. There have been three systematic reviews published to date[22–24] that report outcomes on human participants with chronic pain from dietary interventions, all published in the last 2 years. These reviews report the effectiveness of improved nutrition generally as a pain

* **Corresponding author:** Rowena Field, email: rfie5606@uni.sydney.edu.au

management option, particularly when considering nutrient-dense whole-food diets and the removal of discretionary ultra-processed foods high in sugar and fat. They are unable to clearly point to any specific diet as the best treatment, however. A recent review suggested both the Mediterranean diet and a carbohydrate-restricted diet were promising diets for reducing the impact of chronic pain by either a reduction in inflammation or a reduction in oxidative stress[26]. The authors note, however, that only two studies reviewed were specifically assessing the context of chronic pain (knee osteoarthritis) and the rest were examining participants with metabolic dysregulation (such as elevated cardiovascular risk or obesity).

Nutritional ketosis is achieved through a ketogenic diet by restricting dietary carbohydrates sufficiently to shift cellular energetics from glucose to fat oxidation as the main fuel source[27]. Ketone bodies (β-hydroxybutyrate and acetoacetate) are produced in the liver (ketosis) and delivered via the bloodstream as part of this alternate fuel pathway, providing both a fuel source and a signalling molecule that can modulate many physiological processes[6]. As a signalling molecule, β-hydroxybutyrate is a metabolic intermediary that can act as an endogenous class I and II histone deacetylase inhibitor involved in the regulation of longevity and antioxidant defences, diseases of aging, and also diabetes and cancer[10,28,29]. It acts as a ligand for G-protein-coupled receptors (hydroxycarboxylic acid receptor 2) and free fatty acid receptor 3, which bind short-chain fatty acids, regulate metabolism and play a role in the development of metabolic disease states[28]. Ketone signalling via a ketogenic diet has been reported to beneficially effect physiological processes involved in many disease conditions, including obesity, cancer, diabetes, epilepsy, Parkinson's disease, Alzheimer's disease, multiple sclerosis, peripheral neuropathy, liver disease, inherited metabolic disorders, muscle degeneration, polycystic ovarian syndrome, irritable bowel syndrome, migraine and fibromyalgia[12,30].

Whilst ketogenic diets have reported efficacy clinically for humans in a variety of neurological conditions, the evidence for plausible physiological mechanisms by which the nervous system may be modulated relies heavily on animal models (both *in vivo* and *in vitro*) to explore the mechanistic pathways. The mechanisms suggested are neuroprotective and neuromodulatory, whereby decreasing glycolytic metabolism and shifting to fat oxidation raises ATP and adenosine levels and improves cellular energetics. It also activates multiple signalling pathways involved in the reduction of reactive oxygen species in neurological tissues, increased mitochondrial number and function, synaptic regulation, and inhibition of pro-inflammatory cytokine mediators[18,31–35]. The overall effect would seem to be restoring homeostatic synaptic function and excitability.

To date, there is limited published literature on human clinical trials that examine a ketogenic diet as a treatment for chronic pain. The purpose of this scoping review was to investigate animal models that report outcomes related to the nervous system by changing from a standard animal diet to a ketogenic diet. It includes multiple models of nervous system dysfunction and synthesises the outcomes presented into broader themes by which a ketogenic diet may plausibly modulate biological pathways associated with human chronic pain perception. It also discusses the potential issues with clinical translation from animal models to human models of dietary interventions.

Methods

Protocol

The framework for this review was based on relevant items of the scoping review protocol and PRISMA-ScR checklist from the Joanna Briggs Institute[36,37] to answer the research question: 'How does a ketogenic diet in animal models influence the nervous system?'

Eligibility criteria

Studies were included if they met the following criteria:

1. Mammal models that report an *ad libitum* high-fat, low-carbohydrate ketogenic diet that is ≥7 d (% energy from fat ≥69 % or 3:1 ratio of fat:protein + carbohydrate + fibre + extras) as the intervention. The minimum diet length of 1 week was used to ensure all studies were captured, and was based on similar systematic reviews reporting studies where the minimum reported length of diet was 2 weeks in rat and mouse models assessing both metabolic and nervous system outcomes[38,39].
2. Studies that report objective outcomes related to nervous system function including neuroinflammation.
3. Experimental study designs: longitudinal pre–post intervention trials including randomised controlled trials.

Studies were excluded if:

1. The diets were both high in fat and carbohydrate, carbohydrate levels exceeded 10 % or where the chow was not described, and the ketogenic status could not be confirmed.
2. The diet was not *ad libitum* or provided in the form of whole food, including oral gavage, intraperitoneal models, food extracts or exogenous ketones.
3. The subjects were human or *in vitro* cultures.
4. The model used represented cancer or genetic syndromes.
5. The paper was not in English.

Information sources and search strategy

An electronic database search including Medline, EMBASE, Cochrane Library for controlled trials, AMED via OVID, CINAHL via Ebsco, Web of Science and PubMed was carried out on 5 July 2020 and included dates from database inception to the search date. A preliminary search refined the search strategy, with the key terms outlined in Supplementary Table 1. Additional searches included a Google Scholar search to check identified articles 'cited by' and 'related articles' links, and reference checks on identified articles with subsequent hand search for these and inclusion if they met the criteria. Retrieved references were downloaded into EndNote reference management software (Endnote X7.7.1, Thomson Reuters 2016) and then imported using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

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Study selection and screening

Duplicates were removed, then titles and abstracts were assessed in Covidence by two reviewers independently (R.F. and T.F) against the eligibility criteria. Full texts of identified studies were then screened by two reviewers independently (R.F. and T.F) for final eligibility, with any disagreements resolved by a third reviewer.

Data items

The primary outcomes of interest were changes in nervous system function (such as excitability) or energetics (such as altered substrate measured by blood glucose or ketones levels) that report a plausible biological mechanism by which a ketogenic diet may influence the nervous system. Additional data extracted included: author, year of study, animal, animal variant, chow ratios, disease model and intervention diet length. Critical appraisal of the literature to assess risk of bias was not carried out due to the frequently poor-quality methods employed in animal research. This includes lack of randomisation, lack of blinding and incorrect statistical methods[40,41]. Nervous system outcomes were taken as presented by the study authors.

Data charting process and synthesis of results

Data items were extracted and compiled in an excel spreadsheet. Primary outcomes were reviewed, and a subjective thematic analysis was carried out by R.F. The process of thematic analysis involved building a list of categories that best fit the outcome description given by the study author. These were then further synthesised into broad themes. Studies with more than one relevant theme could be allocated into more than one theme. A random sample of thirty-five studies (20 %) was independently reviewed by T.F to ensure consistency of theme allocation.

Results

A systematic search of the databases retrieved 7045 studies screened for eligibility after duplicates were removed. A total of 341 full-text articles were assessed with a total of 170 meeting the inclusion criteria and included in the scoping review (Fig. 1). Of the ninety-nine studies excluded for being either >10 % carbohydrate or ≤69 % fat, only three studies were described as lower in ketogenic (but still included 32 % carbohydrate, 20 % carbohydrate or 30 % fat). The remaining studies were captured by the search term 'high fat', which retrieved studies high in both fat and carbohydrate designed to produce obesity or metabolic dysfunction.

Characteristics of included studies

The studies comprised 103 rat studies, 63 mouse studies, 2 that included rats and mice, and 1 that included rats and gerbils as well as a canine case study. There was a range of nervous system dysfunction models, including five age-related degeneration[42–46], four Alzheimer's disease[47–50], seven autism[51–57], four cerebral ischaemia[58–61], two pain perception[16,62], twenty-four general central nervous system[63–86], two diabetes[87,88], ninety-one epilepsy[89–179], two metabolic syndrome[180,181], one mild cognitive impairment[182], two multiple sclerosis[183,184], one nerve toxin[185], four optic nerve dysfunction[186–189], two Parkinson's disease[190,191], three peripheral nerve dysfunction[192–194], four spinal cord injury[195–198], three stroke[199–201] and nine traumatic brain injury[202–210]. The length of the dietary intervention ranged from 1 week to 6 months.

Fourteen broad themes involving nervous system function were identified. These themes, the disease models used, and further details are presented in Table 1. Detailed information on individual study characteristics and reported outcomes is compiled in Supplementary Table 2, which references all 170 included studies.

1. *Alterations in cellular energetics and metabolism (reported in twenty-eight studies across nine disease models*[42,43,46,49,63,68,70,72,74–76,83,85,87,91,95,97,108,125,136,142,156,187,188,192,197,202,207]*)*. The reduced glucose consumption of a ketogenic diet resulted in lower glucose availability within the nervous system and a shift to fat-based metabolism with up-regulation of processes required to deliver this alternate energy substrate. Fat-based metabolism was reported to improve energy availability, utilisation and efficiency. It was also reported to reduce low-grade inflammation driven by a low energy state.
2. *Biochemical (reported in three studies in epilepsy models*[102–104]*)*. Elemental changes (P, S, K, Ca, Fe, Cu, Zn and Se) within the hippocampus were assessed via X-ray fluorescence microscopy with significant changes, with a significant decrease in P, K and Zn, and a significant increase in Ca and Se as a result of the ketogenic diet. As hippocampal levels of Ca increase with seizures, these changes did not provide evidence supporting a mechanism for seizure reduction. Additionally, the ratio of absorbance for specific biological macromolecules (such as ketones and lipids) was increased with the possibility of these molecules being involved in anti-seizure mechanism rather than elemental changes.
3. *Cortical/neuronal excitability (reported in fifty-three studies of which forty-nine were epilepsy models*[53,57,67,89–94,104,107,109–111,113–116,118,124,125,127,129,131,135,140–142,144,150–152,154–156,158–164,166,167,170–173,175,177–179,209]*)*. The ketogenic diet was broadly reported to restore the balance of nervous system excitability toward homeostatic levels; however, some studies reported neutral or negative findings[91,93,140,150,151,154,166,175,178]. This category was largely composed of epilepsy models that described reductions in frequency, threshold, duration, latency and spread of seizures. Restoration of circadian rhythms within the brain was also reported.
4. *Epigenetic regulation (reported in thirty studies across nine disease models*[44,55,61,69,72,76,95,97,99,100,105,106,108,122,127,132,135,145,146,149,157,165,172,174,176,177,181,182,192,208]*)*. The genes reportedly altered by the ketogenic diet generally pertained to the disease model being investigated. Overall, they tended to up-regulate beneficial genetic expression regarding neuroinflammation, neurodegeneration and neuroprotection.
5. *Mitochondrial function (reported in eighteen studies across ten disease models*[45,51,52,76,78,97,117,120,134,173,180,184,187,192,199,203–205]*)*. The overall reported benefit to the mitochondria

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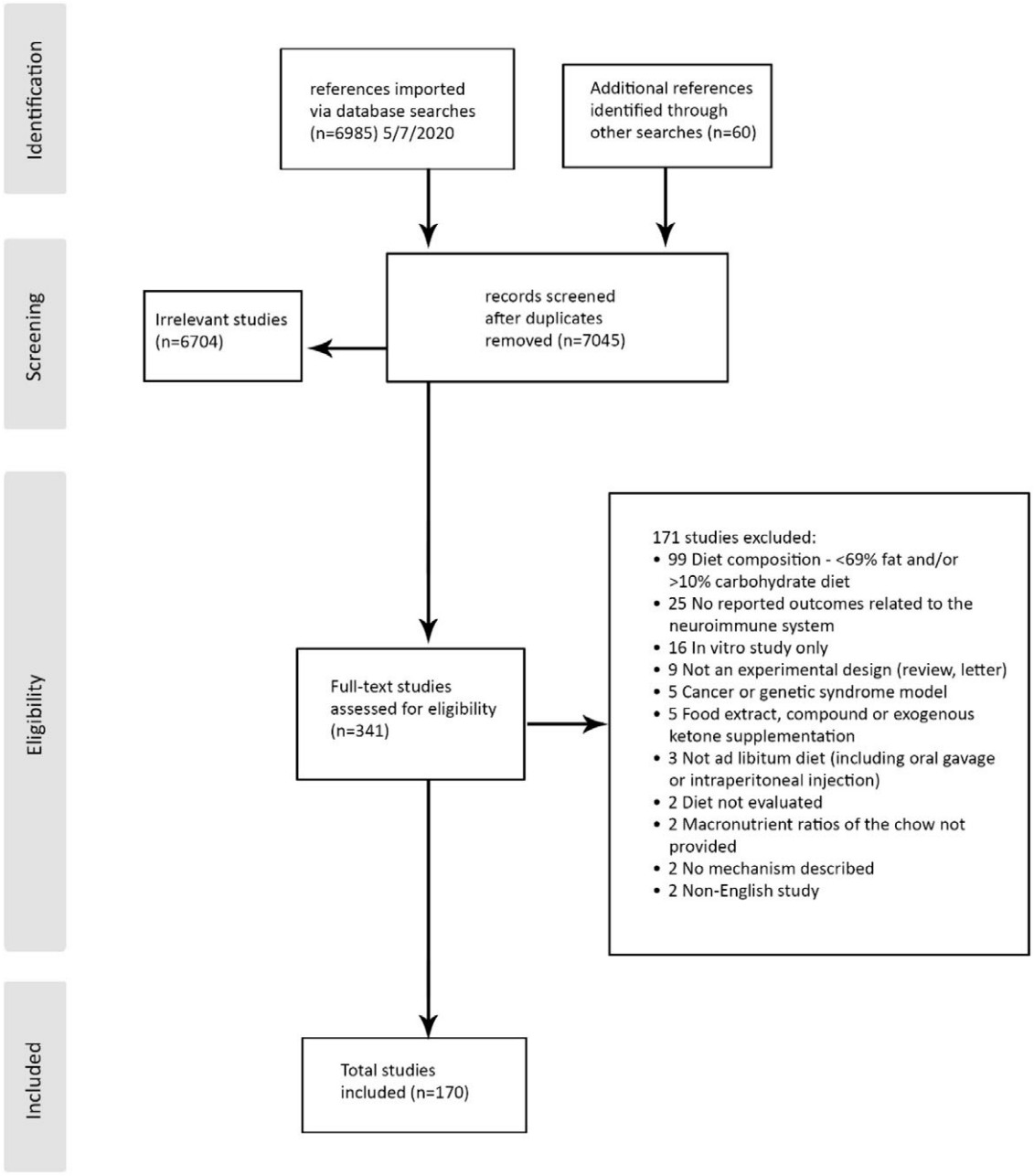

Fig. 1. Inclusion flowchart.

within the nervous system was positive, with increases in number, and improvements in structure and function including energy production and redox balance.

6. *Neuroinflammation (reported in seven studies across six disease models*[123,183,188,191,199,204,206]*)*. Ketones were reported to inhibit the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome expressed in the nervous system and subsequent reduction of the downstream inflammatory signalling pathways it generates. Neuroinflammation was also reportedly reduced through a reduction in reactive oxygen species. Neuroinflammation was frequently reported in terms of signalling pathways, so many of the relevant studies were reported in theme 12.
7. *Neuroplasticity and structural integrity (reported in twenty-six studies across ten disease models*[45,47,50,54,73,77,79,80,124,130,133,134,141,143,144,147,183,184,186,189,193,194,197,199–201]*)*. Improved synaptic plasticity (long-term potentiation) and a reduction of maladaptive plasticity (such as mossy fibre sprouting in epilepsy models) was reported on a ketogenic diet. Other structural changes reported across a range of disease models included: improved myelin formation, reduced axonal degeneration, improved white matter development, reduction in β-amyloid, increased neuronal progenitor cells following seizure, prevention of neuronal loss in the ipsilateral hippocampus, reversal of hippocampal atrophy and lesions, improved neuronal recovery following insult

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when the diet commenced pre-injury, and reduction in retinal ganglion cell loss.

8. *Neuroprotection (reported in six studies across four disease models*[58,59,88,185,190,191]*)*. A reduction of neuronal apoptosis and neuronal death was reported as a result of the diet in a variety of disease models. Protection against seizure was commonly reported in the epilepsy models and reported in theme 3.
9. *Neurotransmitter function (reported in ten studies across four disease models*[45,64,70,74,85,96,98,101,153,190]*)*. Various mechanisms around neurotransmitter production and clearance were reported with proposed benefit from the diet being an improved GABA levels or GABA-to-glutamate ratio. Parkinson's disease models reported improvements around dopamine levels.
10. *Nociception (reported in three studies, two for pain and one for peripheral nerve dysfunction*[16,62,193]*)*. A reduction in both allodynia and thermal pain sensitivity was reported that was not dependent on lowered glucose levels.
11. *Redox balance (reported in fifteen studies across eight disease models*[63,71,78,86,92,120,180,181,186,190,192,195,196,203,210]*)*. Several studies found an improvement in redox balance through either a reduction in nervous system reactive oxygen species or an increase in antioxidant defence.
12. *Signalling pathways (reported in thirty-six studies across eight disease models* [48,54,56,60,61,63,65,66,69,71,82,84,112,119,121,123,125,126,131,135,137–139,143,148,149,161,164,168,169,187,196,198–201]). A variety of signalling pathways were reported depending on the disease model being used. These centred around other key mechanisms such as reduced neuroinflammation, reduced oxidative stress, altered neuronal energy metabolism, reduced cortical excitability and reduced neurodegeneration.
13. *Synaptic transmission (reported in seven studies across three disease models*[42,44,67,95,97,128,178]). Improved clearance and levels of protein transporters for neurotransmitters was reported to improve synaptic transmission. Cortical excitability was described as improved due to a reduction in long-term potentiation, without any change in baseline excitability or impact on normal brain activity. Not all studies noted reduced long-term potentiation[67].
14. *Vascular supply (reported in three studies across three disease models*[48,61,81]). The size of cerebral infarct and oedema was reduced with a ketogenic diet. Alzheimer's models reported increased blood flow providing positive outcomes. In epilepsy, positive outcomes due to a decrease in capillarisation associated with seizures were also reported.

Discussion

The aim of this scoping review was to investigate animal models that report outcomes related to the nervous system by changing from a standard animal diet to a ketogenic diet. We identified fourteen broad themes of biological mechanisms from eighteen different disease models by which a ketogenic diet is reported to influence the nervous system in animal models (Table 1). Multiple themes may be present within a single study, with many of the different mechanisms and pathways reported resulting in similar overarching effects, including reduction of inflammation and oxidative stress, normalisation of neuronal excitability and improved cell viability. The themes outlined are consistent with other broader reviews that included *in vitro* and hypothetical models[211,212]. The purpose of describing these themes was to provide insight into how altering dietary macronutrients to produce ketosis in humans could also plausibly exert influence on the nervous system in a chronic pain model. The ketogenic diet appears to utilise metabolic modulation to engage the reported mechanisms in animal studies, and thus could also potentially facilitate positive changes within a human nervous system that has undergone aberrant neuroplasticity leading to a persistent pain state.

There are many mechanisms presented that fit with current priorities in pain neuroscience research, such as targeting inflammation. An increase in pro-inflammatory cytokines is often seen in chronic lifestyle disease[213], but also frequently occurs with chronic pain[214,215]. The failure of the inflammatory response to resolve perpetuates the development of metabolic diseases, but also potentially contributes to persisting pain by shifting the nervous system towards a pathologically maladapted state[216]. Neuroinflammation is a common finding in many neurological conditions and was frequently reported in the outcomes from the extracted studies. Modulation of neuroinflammation across various models from the ketogenic diet was attributed to as many as nine mechanisms (Supplementary Table 2): (a) suppression of nuclear factor (NF)-kβ resulting in reduced expression of proinflammatory cytokines tumour necrosis factor α (TNF-α), interleukin (IL)-1β and interferon (IFN)-γ[196]; (b) a decrease in hippocampal mRNA levels of IL-1β[106]; (c) reduced pro-inflammatory cytokine hippocampal TNF-α levels with reduced NF-kβ dependant cyclooxygenase (COX)-2 (enzyme for prostaglandin synthesis) signalling pathway[123]; (d) activation of the peroxisome proliferator-activated receptor (PPAR)-γ[161] (a nuclear transcription factor involved in detecting and metabolising lipids) which also suppresses the COX-2 dependant pathway[123] and regulates catalyse expression[126]; (e) central and peripheral suppression of inflammatory cytokines/chemokines coupled with a reduction in reactive oxygen species (ROS)[183]; (f) meeting the cellular energy demand which inhibits AMP-activated protein kinase (AMPK) (which senses and regulates cellular energy levels) and reduces low-energy facilitated inflammation[188]; (g) inhibition of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome through ketone action on hydroxycarboxylic acid receptor 1 (HCAR1)[188,196]; (h) altered NAD+/NADH ratio (which is coupled to glycolysis) and regulates inflammation[63]; and (i) reduced mitochondrial ROS production[199]. The use of a ketogenic diet for chronic pain management could be theoretically targeting any of these mechanisms to lower inflammation and reduce pain perception[4,18,217], and is supported mechanistically by the outcomes from animal research.

Mitochondrial pathology is another theme presented that has been implicated in central sensitisation seen in chronic pain, with dysfunctional mitochondria observed in the muscle cells of fibromyalgia patients[218], and two recent studies reporting between 67 % and 91 % of patients with mitochondrial diseases also reporting chronic pain[219,220]. Given this, strategies to restore or optimise mitochondrial function would be an

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Table 1. Overall themes presented for beneficial ketogenic diet outcomes

Models	Mechanistic theme	Detail
ARD, ALZ, CNS, D, EP, ON, PND, SCI, TBI	Cellular energetics and metabolism	• Reduction in glucose availability with concomitant increase in alternate fuel substrates (ketones, lactate, glutamate) • Adaptive regulation of energy transporters reflecting change in fuels (reduction in glucose transporters and increase in ketone transporters) • Improved cerebral energy metabolism, utilisation and efficiency • Increased energy reserves/ATP • Increased seizure resistance when combined with calorie restriction • Reduction in maladaptation driven by low-energy-facilitated inflammation
EP	Biochemical	• Increased calcium selenium, decreased phosphorus, potassium and zinc areas of hippocampus
AUT, CNS, EP, TBI	Cortical/neuronal excitability	• Balance of excitation and inhibition restored towards more normal levels • Reduction in seizure events, threshold, duration, intensity, latency and spreading. Delayed progression of seizure stage • Restoration of circadian rhythms
ARD, AUT, CI, CNS, EP, MetS, MCI, PND, TBI	Epigenetic regulation	• Modulation of genes for neurotransmitter production and function, synaptic transmission and neuroplasticity • Altered mitochondrial gene expression favouring biogenesis, improved function and efficiency • Up-regulation of genes for brain adaptation following ischaemia • Up-regulation of differentially regulated transcripts encoding energy metabolism enzymes • Up-regulation of intracellular signal transduction pathways • Modulation of genes for inflammatory signalling pathways favouring anti-inflammation • Down-regulation of genes related to apoptosis and neuronal death • Altered gene expression for various factors related to seizure production, ameliorated seizure–induced DNA methylation • Down-regulation of genes related to neurodegeneration
ARD, AUT, CNS, EP, MetS, MS, ON, PND, ST, TBI	Mitochondria	• Increased biogenesis and mass • Improved bioenergetic profile, oxygen consumption and maximal respiration rates • Improved mitochondrial antioxidant defence • Improved mitochondrial autophagy • Decreased percentage of damaged mitochondria post-seizure with increased expression of autophagy proteins and decreased apoptosis
EP, MS, ON, PKD, ST, TBI	Neuroinflammation	• Suppression of inflammatory cytokines/chemokines and reactive oxygen species • Inhibition of the NLRP3 inflammasome • Reduced oedema
ARD, ALZ, AUT, CNS, EP, MS, ON, PND, SCI, ST	Neuroplasticity/structural integrity	• Improved hippocampal synaptic plasticity • Improved myelin formation and white matter development • Neuroanatomical differences with prenatal exposure • Prevention of neuronal loss • Increased neuronal recovery post-seizure • Reduced supragranular mossy fibre sprouting in epilepsy models
CI, D, NT, PKD,	Neuroprotection	• Reduced likelihood of seizure. • Elimination of post-ischaemia hippocampal neurodegeneration • Reduced neuronal death • Attenuated toxicity from a neurotoxin
ARD, CNS, EP, PKD	Neurotransmitter function	• Improved GABA-to-glutamate ratio • Increased dopamine activity in the motor and somatosensory cortex • Altered gut biome resulting in systemic GABA and elevated hippocampal GABA/glutamate levels • Inhibited decrease of striatal dopamine and metabolites
CP, PND	Nociception	• Decreased thermal pain sensitivity • Protection from allodynia
CNS, EP, MetS, ON, PKD, PND, SCI, TBI	Redox balance	• Improved redox state • Improved neurochemical metabolite ratios

Table 1. (*Continued*)

Models	Mechanistic theme	Detail
		• Increase in hippocampal mitochondrial glutathione
		• Improved brain oxidative stress responses
ALZ, AUT, CI, CNS, EP, ON, SCI, ST	Signalling pathways	• Improved neurovascular function via mechanistic target of rapamycin (mTOR) inhibition
		• Increased effector substrates for glutamate, serotonin, dopamine and tryptophan
		• Activation of multiple pathways providing neuroprotection
		• Dietary lipid signalling, with different lipids producing different nervous system outcomes
		• Activation of detoxification pathways
		• Activation of pathways to reduce oxidative stress
		• Activation of pathways impacting circadian timing
		• Activation of multiple pathways involved in cortical excitability and seizure regulation
		• Activation of pathways supressing neuroinflammation
		• Activation of molecules involved in neuronal growth and survival
ARD, CNS, EP	Synaptic transmission	• Restoration of vesicular transporters levels for GABA and glutamate
		• Transmission resistant to low glucose levels and metabolic stress
		• Reduced long-term potentiation that preferentially limits excess excitability whilst preserving normal brain activity
ALZ, CI, CNS	Vascular supply	• Increased cerebral blood flow in ALZ model
		• Decreased capillarisation associated with tumour growth and seizure prevention
		• Reduced infarct size

ARD, age-related degeneration; ALZ, Alzheimer's disease; AUT, autism; CI, cerebral ischaemia; CP, chronic pain; CNS, central nervous system generally; D, diabetes; EP, epilepsy; MetS, metabolic syndrome; MCI, mild cognitive impairment; MS, multiple sclerosis; NT, nerve toxin; ON, optic nerve; PKD, Parkinson's disease; PND, peripheral nerve dysfunction; SCI, spinal cord injury; ST, stroke; TBI, traumatic brain injury.

appropriate pain management strategy[221]. Beneficial outcomes on mitochondria were frequently reported in the extracted studies (Table 1); however, the result is less clear when examining the outcomes of individual studies (Supplementary Table 2). Kephart *et al.*[180] reported no benefit to mitochondrial quality in brain tissue sampled following a long-term ketogenic diet. A study by Lauritzen *et al.*[45] was one of the few to report negative outcomes. This study was designed specifically to examine a mouse model of mitochondrial dysfunction bred to express a mutated mitochondrial DNA repair gene (mutUNG1) designed to represent DNA damage that occurs in neurological disorders. They reported an increase in mitochondrial mass in the hippocampus and upregulated mitochondrial antioxidant defences, which would appear positive; however, this did not correlate with their overall observation of accelerated neurodegeneration from impaired mitochondrial dynamics and function. The context of their experiment becomes important, where the ketogenic diet increased mitochondrial biogenesis, but this increase was of dysfunctional mitochondria, compounding the neurodegeneration and energy demands. This study highlights the difficulty in extrapolating these results to human application. Their research does not necessarily apply to a ketogenic diet applied in the absence of this specific mitochondrial gene mutation, but as the authors[45] conclude, the diet also cannot be considered always beneficial for every type of mitochondrial pathology. Theoretically, the ketogenic diet appears to have potential for pain management through the improvement of mitochondrial function with subsequent reduction of oxidative stress and inflammation. Variability in clinical efficacy is likely to exist due to nuance in the mechanism of mitochondrial pathology.

Difficulty in extrapolating results also exists where an animal is fed the diet, but the analysis occurs in a dissected animal which is no longer a part of a complex adaptive system. One of the inclusion criteria for the current review was that the experiment had to have fed a ketogenic diet to the animal; cell culture and *in vitro* studies were excluded. The lack of an intact noradrenergic system may limit the effect of the ketogenic diet and produce disparate results[164] and may also account for the differences seen between animal and human trials involving ketogenic diets.

Chronic pain involves an increase in neuronal excitability[222,223], with links suggested between these mechanisms and those involved in seizures, and the use of anticonvulsant medications to treat neuropathic pain[18]. A ketogenic diet has been widely used clinically as a treatment for epilepsy with several trials in adults[15] as well as children[224]. A similar interpretive difficulty lies in the animal research for epilepsy where clinical human trials report generally favourable outcomes, but the animal research results can range between anticonvulsant to pro-convulsant outcomes[91,166,175] (Supplementary Table 2). Again, experiment design becomes important, with the eighty-nine epilepsy studies including: different animal models (species, strain and age), multiple different seizure induction models (using different chemicals with different target receptors, and some using electrical shock), inconsistent levels of ketosis achieved, different chow content and quality, different chow quantity (with some diets employing calorie restriction in conjunction with the ketogenic diet), different lengths of dietary intervention, mismatched animal weight between groups resulting from different diets[150], and different

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dietary applications where the diet could be started pre-seizure/brain injury or after the event. Despite commonalities, translating the proposed neuromodulatory mechanisms from the animal epilepsy research to clinical chronic pain conditions requires more nuance and may explain variable clinical results in any human trials.

Neurotransmitter function was frequently reported in the included studies as a change within the nervous system favouring a reduction or restoration of normal levels of neuronal excitability. The mechanism reported was improved GABA-to-glutamate ratios usually via increased GABA (inhibitory) and/or decreased glutamate (excitatory) levels, with outcomes being a reduction in various seizure metrics in the animals tested. The research exploring the relationship between chronic pain and neurotransmitter levels is inconsistent. There is evidence supporting motor cortex disinhibition that is more pronounced in neuropathic pain[222]; however, whether this is due to a loss of GABAergic inhibition, as has been suggested, is still unclear. A recent systematic review reported altered neurotransmitter levels demonstrated in a small number of human chronic pain trials. There were increased levels of Glx (glutamate and glutamine combined) reported, but no corresponding reduction in GABA as might be expected[225]. The authors reported that different pain conditions may present with unique neurometabolite signatures, but the research was limited by inadequate reporting and standardisation of magnetic resonance spectroscopy techniques used.

A further variable that may contribute to the inconsistencies reported is that of the chow. Problems exist where the control diets are not matched appropriately to the ketogenic chow. Differences in vitamins, minerals and fibre exist between the diets as well as the macronutrient properties, limiting the ability to assess the ketogenic component of the diet. A number of issues also exist with the commercial rodent ketogenic diet formulations, including restriction of protein, choline deficiency[226] and poor-quality fats (such as hydrogenated vegetable oils) rather than fats with a more beneficial inflammatory profile (such as omega-3)[227].

The evidence presented in animal models supporting positive changes from a ketogenic diet, such as seen with anti-inflammatory mechanisms, appears compelling. However, the reported outcomes overall are often inconsistent and ambiguous[67], and there are many difficulties when extrapolating from animal models to human models of chronic pain[228]. The use of specific animal strains and sex may reduce the heterogeneity and increase the likelihood of detecting an effect, but may be poor representations of the diversity in target human pain populations[229]. These translational issues could be explored by also including natural animal models (such as using the ketogenic diet on naturally occurring pain presentations in domestic animals)[229] as well as more consistency in experimental design, and reporting which more clearly acknowledges the limitations of the research. These strategies may allow the data to better inform human clinical trials of chronic pain.

Conclusion

Fourteen broad themes were identified from the literature outlining how a ketogenic diet influences nervous system function from animal models. The mechanisms presented centred around the reduction of inflammation and oxidative stress as well as a reduction in nervous system excitability. These mechanisms are potential drivers of chronic pain, and treatment strategies which target these have implications for chronic pain management. Given the multiple potential mechanisms presented, it is likely that many of these are involved synergistically and undergo adaptive processes within the human body, and controlled animal models that limit the investigation to a particular pathway in isolation may reach differing conclusions. Attention is required when translating this information to human chronic pain populations owing to the limitations outlined from the animal research.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S0954422421000214

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