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Review

# Functions and effects of creatine in the central nervous system

Robert H. Andres[a], Angélique D. Ducray[a], Uwe Schlattner[b,c], Theo Wallimann[b], Hans Rudolf Widmer[a,*]

[a] Department of Neurosurgery, University of Berne, Inselspital, CH-3010 Berne, Switzerland
[b] Institute of Cell Biology, ETH Zurich, Hoenggerberg, CH-8093 Zurich, Switzerland
[c] Laboratory of Fundamental and Applied Bioenergetics, INSERM E0221, Joseph Fourier University, F-38041 Grenoble, Cedex 9, France

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ABSTRACT

Creatine kinase catalyses the reversible transphosphorylation of creatine by ATP. In the cell, creatine kinase isoenzymes are specifically localized at strategic sites of ATP consumption to efficiently regenerate ATP *in situ* via phosphocreatine or at sites of ATP generation to build-up a phosphocreatine pool. Accordingly, the creatine kinase/phosphocreatine system plays a key role in cellular energy buffering and energy transport, particularly in cells with high and fluctuating energy requirements like neurons. Creatine kinases are expressed in the adult and developing human brain and spinal cord, suggesting that the creatine kinase/phosphocreatine system plays a significant role in the central nervous system. Functional impairment of this system leads to a deterioration in energy metabolism, which is phenotypic for many neurodegenerative and age-related diseases. Exogenous creatine supplementation has been shown to reduce neuronal cell loss in experimental paradigms of acute and chronic neurological diseases. In line with these findings, first clinical trials have shown beneficial effects of therapeutic creatine supplementation. Furthermore, creatine was reported to promote differentiation of neuronal precursor cells that might be of importance for improving neuronal cell replacement strategies. Based on these observations there is growing interest on the effects and functions of this compound in the central nervous system. This review gives a short excursion into the basics of the creatine kinase/phosphocreatine system and aims at summarizing findings and concepts on the role of creatine kinase and creatine in the central nervous system with special emphasis on pathological conditions and the positive effects of creatine supplementation.


## Contents

1. Introduction ..... 330
1.1. The creatine kinase/phosphocreatine system ..... 330
1.2. CK microcompartments and high-energy phosphate channeling ..... 330
1.3. Expression of creatine kinase isoenzymes ..... 330
1.4. The CK system and brain function ..... 331
1.5. Brain energetics ..... 332
1.6. Brain creatine synthesis and uptake ..... 332
1.7. Non-energy-related effects of creatine ..... 332

*Abbreviations:* 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; AD, Alzheimer's disease; AGAT, arginine:glycine amidino transferase; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BBB, blood–brain barrier; BB-CK, brain-specific isoform of CK; ChAT, choline acetyltransferase; CK, creatine kinase; CMT, Charcot-Marie-Tooth disease; CNS, central nervous system; Cr, creatine; CRT, creatine transporter; GAA, guanidino acetate; GAMT, S-adenosyl-L-methionine: *N*-guanidinoacetate methyltransferase; GPA, beta-guanidino propionic acid; HD, Huntington's disease; LS, Leigh syndrome; MB-CK, heterodimeric isoform of CK; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes syndrome; MHC, myosin heavy chain; mHH, mutant huntingtin protein; MM-CK, muscle-specific isoform of CK; MPP+, 1-methyl-4-phenyl pyridinium; MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; PD, Parkinson's disease; PET, positron emission tomography; $P_i$, inorganic phosphate; PTSD, post-traumatic stress disorder; sMt-CK, sarcomeric mitochondrial CK; TBI, traumatic brain injury; uMt-CK, ubiquitous mitochondrial CK; UPDRS, unified Parkinson's disease rating scale.

* Corresponding author. Tel.: +41 31 632 2770; fax: + 41 31 382 2414.
*E-mail address:* hanswi@insel.ch (H.R. Widmer).

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2. Effects of creatine on cognitive processes and in psychiatric disorders ... 332
3. Inborn errors of metabolism ... 334
3.1. Mitochondrial encephalomyopathies ... 334
3.2. Creatine-deficiency syndrome with defects in creatine synthesis and transport ... 334
3.3. Hyperammonemia ... 335
4. Creatine and acute neurological disorders ... 335
4.1. Cerebral ischemia and stroke ... 335
4.2. Traumatic brain and spinal cord injury ... 335
4.3. Injury of the peripheral nerve ... 335
5. Creatine and neurodegenerative diseases ... 335
5.1. Alzheimer's disease ... 335
5.2. Amyotrophic lateral sclerosis ... 336
5.3. Charcot-Marie-Tooth disease ... 336
5.4. Huntington's disease ... 336
5.5. Parkinson's disease ... 338
6. Creatine and cell replacement strategies ... 338
7. Conclusions and outlook ... 339
Conflict of interest ... 339
Acknowledgements ... 339
References ... 339

## 1. Introduction

Cellular energy demand and supply are balanced and tightly regulated for economy and efficiency of energy use. Cells with high and fluctuating energy requirements, such as neurons, may increase the rate of ATP hydrolysis within seconds by several orders of magnitude, but intracellular ATP levels remain amazingly constant. This stability paradox [89,90] can be explained by the action of immediately available, fast and efficiently working energy supporting and back-up systems that connect sites of energy consumption with those of energy production via phosphoryl transfer networks [65,64,148,199]. In this respect, creatine (Cr) and the creatine kinase/phosphocreatine (CK/PCr) system have recently received increasing attention. A growing number of reports now provide evidence for the eminent importance of the CK/PCr-system and Cr metabolism for normal function of the brain, as well as under neuropathological conditions. Hence the present review aims at summarizing the function and role of the CK/PCr-system in the brain and spinal cord. We tried as much as possible to incorporate the most recent work in the field. For a more extensive coverage of the literature on Cr and the CK/PCr-system, the reader is referred to the following review articles by Brosnan and Brosnan [40], Schlattner et al. [159], Wallimann et al. [194,196], and Wyss and Kaddurah-Daouk [205].

### 1.1. The creatine kinase/phosphocreatine system

Creatine (*N*-aminoiminomethyl-*N*-methylglycine) is a guanidino compound synthesized from the amino acids arginine, glycine and methionine. Cr is taken up in diets containing fresh meat or fish. In addition, Cr can be endogenously synthesized by the liver, kidney, pancreas, and to some extent in the brain (see Section 1.6). CK, catalyzing the reversible transfer of the *N*-phosphoryl group from PCr to ADP to regenerate ATP, is a major enzyme of higher eukaryotes that deal with high and fluctuating energy demands to maintain cellular energy homeostasis and to guarantee stable, locally buffered ATP/ADP ratios [24,129,150,151,190,193,199,207]. The interplay between cytosolic and mitochondrial CK isoenzymes (see Section 1.3) accomplishes multiple roles in cellular energy homeostasis [97,148,161,159,160,197,199]. Both isoenzymes contribute to the build-up of a large intracellular pool of PCr that represents an efficient temporal energy buffer and prevents a rapid fall in global ATP concentrations upon cell activation or sudden stress conditions [129], when the cytosolic CK equilibrates the cytosolic overall ATP/ADP ratio. Due to the specific localization of mitochondrial and cytosolic CK isoenzymes, the much faster diffusion rate of PCr as compared to ATP [163,189], and the significantly higher diffusion rate of Cr compared to ADP [100], the CK/PCr-system make available for a spatial "energy shuttle" or "energy circuit", bridging sites of ATP generation with sites of ATP consumption (Fig. 1).

### 1.2. CK microcompartments and high-energy phosphate channeling

For the understanding of the functioning of the CK/PCr-circuit, the presence of subcellular CK compartments are of importance. For example, a significant fraction of cytosolic CK is structurally and functionally associated or co-localized with different, structurally bound ATPases. These ATPases include, (i) different ion pumps in the plasma membrane, (ii) the actin-activated myosin ATPase of the contractile apparatus in muscle, where CK is located at the sarcomeric M-band and I-band of the myofibrils, and (iii) the calcium pump of the muscular sarcoplasmic reticulum. In all these cases, PCr is used for local *in situ* regeneration of ATP, which is directly channeled from CK to the consuming ATPase. At the ATP-generating side, a part of cytosolic CK is associated with glycolytic enzymes, and even more importantly the mitochondrial proteolipid complexes containing ubiquitous mitochondrial CK (uMt-CK) are coupled to oxidative ATP production (Fig. 1).

### 1.3. Expression of creatine kinase isoenzymes

Tissue- and compartment-specific isoenzymes of CK do exist which is crucial to their functions in cellular energy metabolism [68]. Most vertebrate tissues express two CK isoenzyme combinations, either dimeric, cytosolic, muscle-type MM-CK together with mostly octameric sarcomeric mitochondrial sMt-CK, or alternatively, brain-type BB-CK, together with uMt-CK [199]. The CK isoenzyme combination, MM-CK with sMt-CK, is expressed in differentiated sarcomeric muscle, cardiac [69] and skeletal [203]. On the other hand, the combination BB-CK with uMt-CK is prominently expressed in brain [99], neuronal cells [39], retina photoreceptor cells [198,202], hair cell bundles of the inner ear [168], smooth muscle [94], kidney [81], endothelial cells [53], spermatozoa [100] and skin [158]. CK isoforms were shown to be present through-

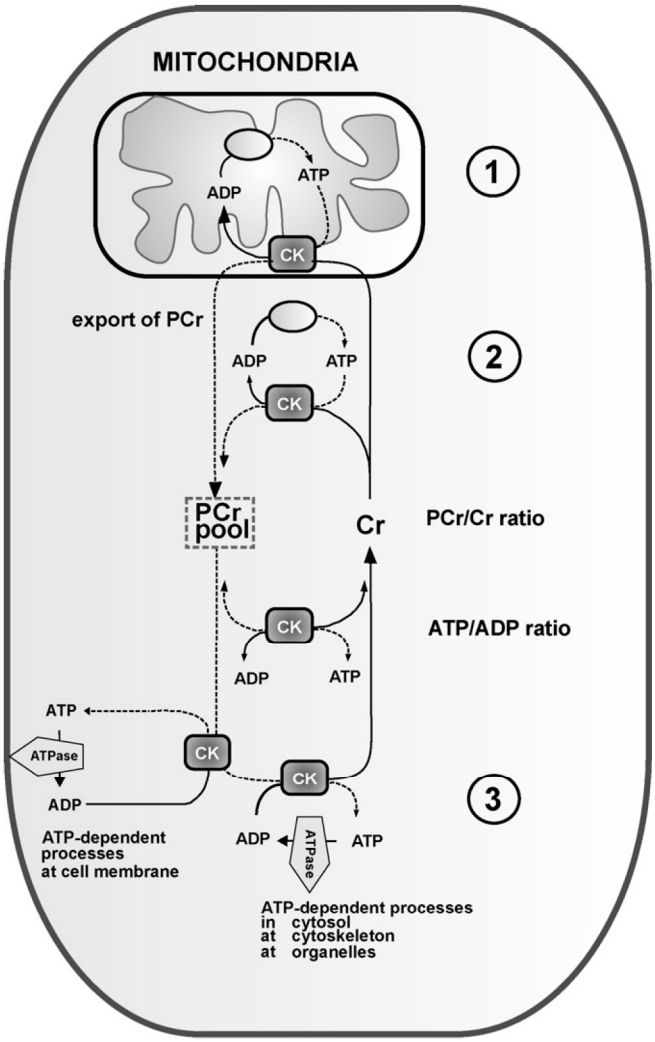


**Fig. 1.** Schematic drawing of the creatine kinase/phosphocreatine (CK/PCr) shuttle in cells: Creatine (Cr) that was taken up into the cell via Cr transporters is transformed to the high-energy compound PCr by either mitochondrial CK coupled to oxidative phosphorylation (1) or by cytosolic CK coupled to glycolysis (2). Mitochondrial CK is located in the intermembrane space of mitochondria and transphosphorylates mitochondrially generated ATP into PCr, which then leaves the mitochondria. The cytosolic CK transphosphorylates glycolytically generated ATP into PCr that is also fed into the PCr pool. PCr is then used to buffer cytosolic ATP/ADP ratios and for local ATP consumption (3), e.g., by cytosolic metabolic enzymes, ATP-requiring contractile processes or cell motility, organelle transport or ATP-dependent cell signaling (middle) or at the cell membrane by ATP-requiring ion pumps, ATP-gated ion-channels or ATP-regulated receptors (left). Hence, the energy producing and consuming terminals of the shuttle are connected via PCr and Cr.

out the central and peripheral nervous system in the fetal rat brain [48,91,99]. Using Western blot analysis, we were able to show high levels of BB-CK and uMt-CK expression in human fetal spinal cord [58], rhombencephalon, ventral mesencephalon, ganglionic eminence and cerebral cortex (Fig. 2). Hybrid cytosolic MB-CK, on the other hand, is expressed only transiently during muscle differentiation but persists at low levels in adult cardiac muscle (for reviews see [199,195,207]).

Octameric uMt-CK is localized in the cristae, as well as in the intermembrane space of mitochondria, preferentially at the contact sites between inner and outer mitochondrial membrane [95,156,159,160,202,207] (Fig. 1). Mitochondrial and cytosolic CK have diverged million years ago [66], suggesting that compartmentalized CK isoenzymes have evolved very early during evolution in the context of functional coupling between uMt-CK and oxida-

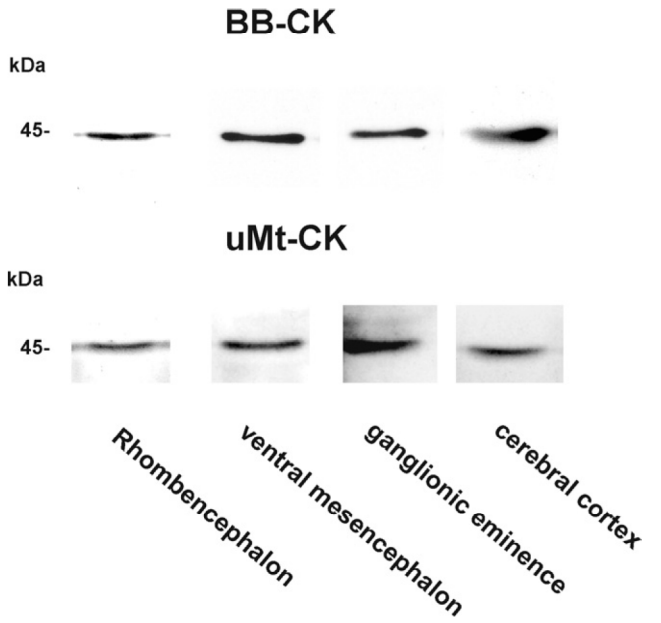


**Fig. 2.** Representative Western blots for cytosolic brain-specific (BB-CK) and ubiquitous mitochondrial (uMt-CK) creatine kinases in human fetal CNS (about 8 weeks post-conception). Both isoforms of creatine kinases were found to be expressed in hindbrain (rhombenecephalon), midbrain (ventral mesencephalon) and forebrain (ganglionic eminence, cerebral cortex). Thus, the enzymatic preconditions for a compartmentalized PCr/Cr-circuit working in brain are given already at an early state of fetal development in humans.

tive phosphorylation [101,149,190] and metabolite channeling [157,159,160].

### 1.4. The CK system and brain function

The importance of the CK system for brain function has been highlighted by experiments using either CK knockout mice or by depletion of brain Cr by pharmacological intervention. Mice with a gene knockout of cytosolic BB-CK showed diminished open-field habituation, a slower learning curve in the water maze, and demonstrated a loss in hippocampal mossy fiber connections [96]. Undetectable PCr and 30% reduced Cr levels in the brain of double knockout transgenic mice, lacking both BB-CK and uMt-CK, have been reported [92]. These CK double knockout mice showed a much more severe phenotype, compared to the single CK isoenzyme knockout mice, since obviously, the lack of cytosolic BB-CK can somehow to some extent be compensated by the presence of mitochondrial uMt-CK and vice versa. The CK double knockout mice showed significantly reduced body and brain weights as compared to wild-type controls and were also behaviorally affected with severely impaired spatial learning, a lower nest-building activity and a diminished acoustic startle reflex [176]. Feeding of normal mice with the Cr analog, beta-guanidino propionic acid (GPA), a competitive inhibitor of the creatine transporter (CRT), resulted in a significant decrease of total Cr pools in muscle and brain, resulting in a muscle and behavioral phenotype [128]. In humans, new creatine-deficiency syndromes, affecting either endogenous Cr synthesis or Cr transport, have been discovered recently (for review see [156]). Patients suffering from this syndrome do have an almost complete lack of Cr in the brain and present with severe neurological symptoms, such as developmental and speech delay, epileptic seizures, autism and severe mental retardation (for details see below). Hence, either ablating the CK isoenzymes or inducing a marked reduction of their substrate in the brain, lead to similar and rather severe phenotypes. These observations provide strong

evidence for the important physiological significance of the CK/PCr-system for normal brain function and indicate a need for a better understanding of Cr metabolism in the human body and particularly in the brain (for review see [205]).

### 1.5. Brain energetics

Importantly to note, the brain, which constitutes only about 2% of the body mass, may spend up to 20% of the body's energy consumption [169]. A very high turnover of ATP is therefore necessary to maintain electrical membrane potentials, as well as signaling activities of the central and peripheral nervous system. Hence, energy production via oxidative phosphorylation and thus the production of ATP and PCr are critical to cerebral function. During physiological function of neurons, rapid changes in ATP demands are occurring while cellular energy reserves are small. An effective coupling of ATP-generating and ATP-consuming processes is needed to maintain a sufficiently high-energy transfer since cellular processes are widely distributed and sites of high-energy consumption are often localized at remote locations from the neuronal cell body, i.e., synapses [6]. For this reason, the CK/PCr-system is assumed to play a critical function in neuronal ATP metabolism [71,86]. In line with this notion, several reports have demonstrated that the CK/PCr-circuit plays a key role in the energy metabolism of the brain and spinal cord [39,45,86,195,206]. Consequently, Cr depletion in brain is associated with disruption of neuronal functions, e.g., loss of hippocampal mossy fiber connection [92], and changes in mitochondrial structure, showing intramitochondrial uMt-CK-rich inclusion bodies [208] that are typical for several clinical pathological conditions, such as encephalomyopathies and mitochondrial myopathies (for review see [201]). As mentioned above, patients with Cr-deficiency syndrome show mental retardation, speech delay, autism and even brain atrophy [175].

### 1.6. Brain creatine synthesis and uptake

Alimentary Cr, present in fresh fish and meat, is taken up by an intestinal CRT [138] and transported into the blood stream, where it mixes with endogenously synthesized Cr. Approximately 50% of daily Cr requirement in humans (totaling 3–4 g of Cr/day) is endogenously synthesized by a two-step synthesis involving the enzymes arginine:glycine amidino transferase (AGAT), producing guanidino acetate (GAA) as an intermediate, and S-adenosyl-L-methionine:*N*-guanidinoacetate methyltransferase (GAMT). The liver is the main organ of endogenous Cr synthesis. To get into the brain, Cr has to pass the blood–brain barrier (BBB), where CRTs are expressed and localized on the luminal and basal side of microcapillary endothelial cells, but not in the astrocytes sitting on these microcapillaries [36,37]. Since the latter are lined with astrocytic feet, which apparently do not express CRT, the restricted transport of Cr from the blood through the BBB into the brain might only be possible through the limited surface of microcapillaries that are not covered by astrocytic endings (for discussion see [35]). This may be an explanation why Cr uptake into the brain and saturation of the endogenous Cr pool takes much longer, as compared to muscle [93]. After passaging through the BBB, Cr is then actively taken up from the extracellular fluid of the brain, by those cells that express the CRT, i.e., neurons and oligodendrocytes, but not astrocytes, which as known up to date are lacking the CRT [36,37,134] (see Fig. 3). In neural cells, Cr is charged-up by CK to high-energy PCr (for review see [205]). AGAT and GAMT can be detected in the embryonic [37] as well as in the adult [36] brain. Hence, there seems to be a potential for endogenous Cr synthesis in the brain [36]. Notably, AGAT and GAMT are not present only in astrocytes, but also in neurons and oligodendrocytes, giving the potential of Cr synthesis to all main cell types of the brain. This does not seem true for CRT, that is not expressed in astrocytes. Trafficking of Cr synthesized by astrocytes between astrocytes and neurons or oligodendrocytes has been suggested [36,184] (Fig. 3). Furthermore, a recent finding demonstrated that Cr is not only synthesized and taken up by neurons, but also released in an action-potential dependent, excitotic manner, providing strong evidence for its role as a neuromodulator in the brain [5]. Notably, a number of important questions, concerning details of Cr metabolism, like regulation of trans-cellular Cr transport, uptake of Cr into the brain and intracellular trafficking and excitotic release of Cr after neuronal stimulation inside the brain, have still to be clarified in more detail.

### 1.7. Non-energy-related effects of creatine

The view that Cr exerts its functions exclusively via effects in cellular energy metabolism [205] and by enhancing the cellular energy status [82] cannot explain a number of recently reported findings (see below). Hence, Cr is assumed to have additional functions in the CNS. For example, a direct anti-apoptotic effect of elevated cellular Cr levels has been reported. In combination with the action of uMt-CK inside mitochondria, Cr prevented or delayed mitochondrial permeability transition pore opening, an early event in apoptosis [56,133]. Moreover, Cr supplementation was demonstrated to have antioxidant properties via a mechanism involving a direct scavenging of reactive oxygen species [164] or alternatively, reducing the production of mitochondrially generated reactive oxygen species. The latter is facilitated by the stimulatory effects of Cr on mitochondrial respiration [101] that allows for efficient recycling of ADP inside mitochondria by uMt-CK, leading to tight coupling of mitochondrial respiration with ATP synthesis and suppression of reactive oxygen species formation [128]. Notably, protective effects of Cr against oxidant and UV stress has been detected in keratinocytes and on human skin [114]. Furthermore, Cr was reported to normalize mutagenesis of mitochondrial DNA and its functional consequences caused by UV irradiation of skin cells [23]. These findings point to effects of Cr for suppression of the generation of reactive oxygen species that lead to cell damage and inactivation of CK. Another recent study provided evidence that Cr-mediated neuroprotection can occur independent of changes in the bioenergetic status but rather by effects on cerebral vasculature leading to improved circulation in the brain [139]. Finally, a recent study demonstrated that Cr is able to protect cultured cells from hyper-osmotic shock by means of a significant increase of Cr uptake into cells, indicating that Cr can act as a compensatory osmolyte [4]. Indeed, Cr has been suggested as one of the main brain cell osmolytes based on experiments using hypo-osmotic perfusion of cortical brain tissue [33,34].

## 2. Effects of creatine on cognitive processes and in psychiatric disorders

High expression of CK isoenzymes has been detected in hippocampal pyramidal cells, which are involved in learning and memory [99]. This observation hints to the idea that the CK/PCr-system plays an essential role for these cells and that Cr supplementation may lead to improved functions of these systems. Indeed, positive effects of orally administered Cr on mental performance have been reported in healthy volunteers in a controlled double-blinded study [201]. Using infrared spectroscopy, the authors found correspondingly increased blood oxygenation in the Cr-treated group. Moreover, a double-blinded study investigating Cr supplementation on healthy vegetarians, which have typically a reduced nutritional Cr supply, revealed significantly bet-

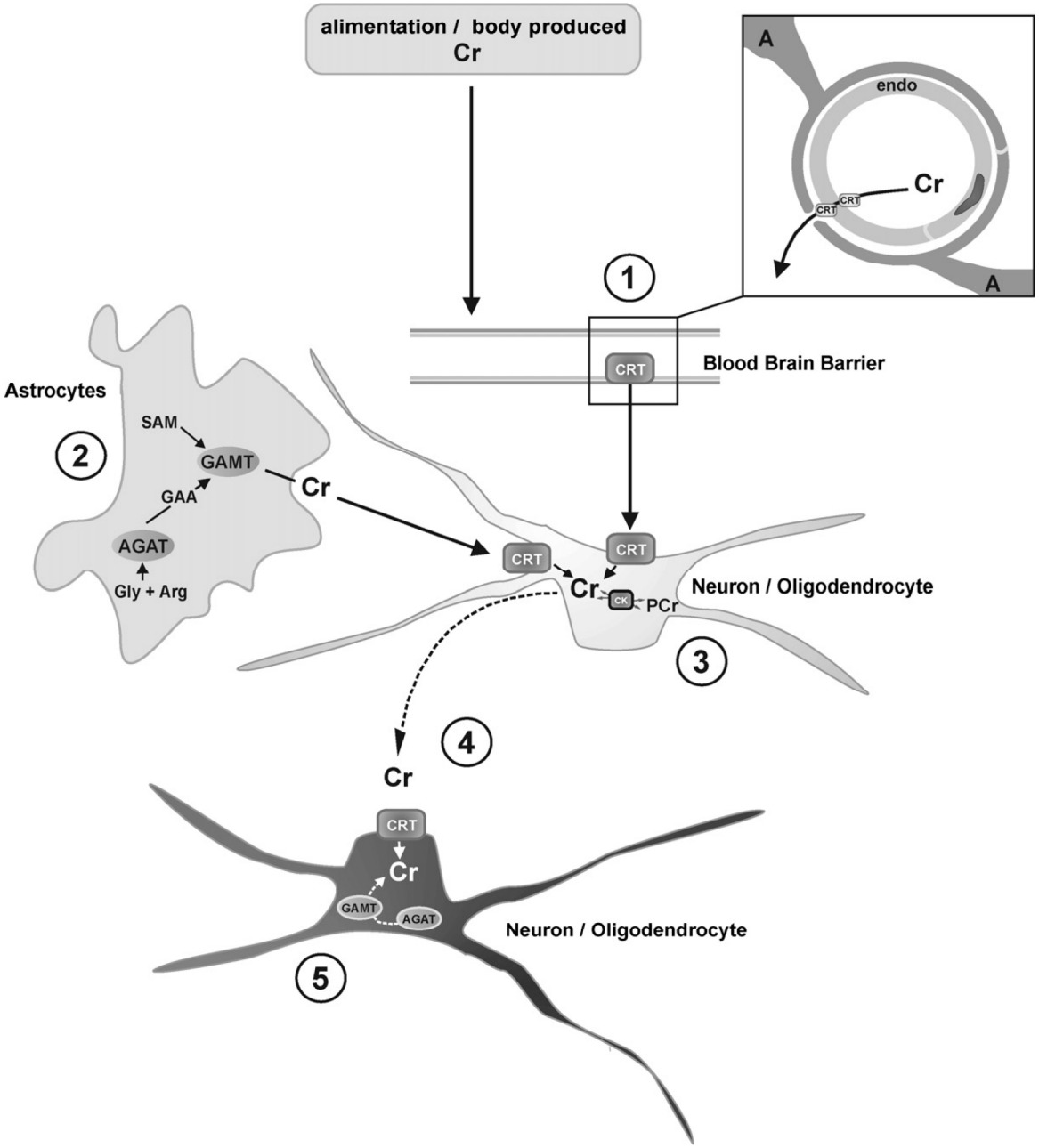


**Fig. 3.** Simplified drawing of the creatine transport to neurons in the brain: Creatine (Cr) taken up by the gut from alimentary sources entering the blood via an intestinal creatine transporter (CRT) or synthesized endogenously by the body is transported through the blood stream to the brain where it needs to pass the BBB via a specific CRT localized in endothelial cells of microcapillaries (1). In fact, CRT is expressed on luminal and basal sides of endothelial cells (endo). The microcapillaries are lined with astrocytic feets (A), not expressing CRT, and Cr is assumed to pass from blood into the brain through the surface not covered by astrocytic endings (enlarged view in insert; for details see [35]). An additional source of Cr for neurons is constituted by astrocytes, involving the enzymes AGAT and GAMT (2). Cr is then taken up by neurons that express CRT (3) and can made available to other neurons by means of exocytotic release (4). Note that in contrast to astrocytes that are devoid of CRT, but able to synthesize Cr endogenously, neurons and oligodendrocytes express CRT and thus can take up Cr from extracellular space. AGAT and GAMT are not present only in astrocytes, but also in neurons and oligodendrocytes (5), giving the potential of creatine synthesis to all main cell types of the brain.

ter results in intelligence test and working memory performance in the Cr-treated subjects as compared to controls [142]. In a most recent test, Cr supplementation (4 × 5 g Cr/day for 7 days) prior to 18–36 h of sleep deprivation was shown to significantly improve the performance of complex central executive tasks [125,124]. Thus, in can be concluded that Cr supplementation enhances brain function under normal and stress conditions. This may be relevant for promoting Cr supplementation as a brain performance-enhancing nutritional supplement for humans. Table 1 summarizes clinical studies investigating the effects of Cr on brain function.

Post-traumatic stress disorder (PTSD) is an anxiety disorder that can develop in persons who experienced highly traumatic situations. PTSD is linked to structural and neurochemical changes particularly in the limbic system, postulated as a substrate for stress-induced alterations in affective behavior [167]. Decreased Cr levels have been measured in the brains of patients suffering from anxiety disorders [49]. Consequently, Cr supplementation had beneficial effects in treatment resistant PTSD patients, resulting in relieved symptoms, as well as improved sleep and depression parameters [7] (Table 2). Furthermore, in a patient suffering from

**Table 1**
Creatine in clinical trials for assessment of brain function

| Study | Subjects | Treatment | Randomized regimen trial | No. of subjects | Efficacy | Safety |
|---|---|---|---|---|---|---|
| Watanabe et al. [201] | Healthy | 8 g/d for 5 d | Yes | 24 | Reduction of mental fatigue. Increased brain oxygen utilization | n.a. |
| Rae et al. [142] | Vegetarians | 5 g/d for 6 w | Yes | 45 | Benefits on mental performance | n.a. |
| Valenzuela et al. [187] | Healthy | 5 w memory training elderly | Yes no creatine | 20 | Elevated creatine brain levels | n.a. |
| Gualano et al. [80] | Healthy | 10 g/d for 3 m males | Yes | 22 | Improvement in glucose tolerance with combined aerobic training | Yes |

Abbreviations: d: day; m: month; n.a.: not addressed; w: weeks.

**Table 2**
Creatine in clinical trials for other neuropathological conditions

| Study | Disease state | Treatment regimen | Randomized trial | No. of subjects | Efficacy | Safety |
|---|---|---|---|---|---|---|
| Stockler et al. [174] | GAMT-D | 4 g/d for 25 m | No | 1 | Normalization of brain creatine | Yes |
| Mercimek-Mahmutoglu et al. [126] | GAMT-D | 0.3–0.8 g/kg per day for 6–24 m | No | 18 | Normalization of brain creatine improvement in behavior but no effects on active speech | n.a. |
| Bianchi et al. [25] | GAMT-D | 0.8 g/kg per day for 12 m | No | 1 | Increase in brain creatine | n.a. |
| Verbruggen et al. [192] | GAMT-D | 0.375 g/kg per day for 7 m | No | 1 | Increase in brain creatine | n.a. |
| Komura et al. [106] | LS | 0.2 g/kg per day for 2 w 0.08 g/kg per day for 4 m | No | 1 | Improved motor skills, and respiratory and cardiac functions | Yes |
| Barisic et al. [17] | MELAS | 20 g/d for 12 d 5 g/d thereafter 28 m | No | 1 | No seizures Improved vocabulary | Yes |
| Komura et al. [105] | MELAS | 0.13 or 0.14 g/kg per day | No | 2 | Improved muscle performance | Yes |
| Amital et al. [7] | PTSD | 3 g/d for 1 w 5 g/d thereafter for 3 w | No | 1 | Benefits on quality of life | n.a. |
| Sakellaris et al. [147] | TBI | 0.4 g/kg per day for 6 m | Yes | 39 | Improved cognitive, self-care communication and behavior functions | Yes |

Abbreviations: d: day; GAMT-D: S-adenosyl-methionine-guanidinoacetate *N*-methyltransferase deficiency; LS: Leigh syndrome; m: month; MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes syndrome; n.a.: not addressed; PTSD: post-traumatic stress disorder; TBI: traumatic brain injury; w: weeks.

PTSD, co-morbid depression and fibromyalgia, Cr treatment caused improvement of symptoms [8].

## 3. Inborn errors of metabolism

### 3.1. Mitochondrial encephalomyopathies

In general, mitochondrial encephalomyopathies are a heterogeneous group of disorders characterized by a broad range of biochemical and genetic mitochondrial defects as well as variable types of inheritance. Mitochondrial myopathy, encephalopathy, lactic acidosis with stroke-like episodes (MELASs) syndrome is one of the most frequent, maternally inherited mitochondrial disorders. In the few clinical trials reported on MELAS patients, Cr supplementation resulted in a normalization of seizures and the patient also showed an improved vocabulary. Furthermore, an increase in muscle performance has been observed in another patient [17,105] (Table 2). Notably, Cr administration resulted in a reversal of the paracrystalline intramitochondrial inclusions in the muscle, which were shown to consist mainly of crystallized uMt-CK [173,185]. In Leigh syndrome (LS), patients suffer from characteristic focal necrotizing lesions in one or more regions of the central nervous system, including the brainstem, thalamus, basal ganglia, cerebellum, and spinal cord. Hence, clinical symptoms depend on which of the listed areas of the central nervous system are involved. The most common underlying cause for LS is a defect in oxidative phosphorylation [51]. In a recent case report, oral Cr supplementation was shown to improve behavioral as well as physiological functions of a child suffering from LS [106] (Table 2). Very recently, Rodriguez and co-workers reported that a combination therapy (creatine monohydrate, coenzyme Q10, and lipoic acid) favorably influenced surrogate markers of cellular energy dysfunction in an inhomogeneous population of patients with mitochondrial cytopathies. The outcome of this randomized, double-blind, placebo-controlled, crossover study design suggests that targeting the final common pathway of mitochondrial dysfunction positively influences the course of the diseases [144].

### 3.2. Creatine-deficiency syndrome with defects in creatine synthesis and transport

A deficiency of Cr in the brain is involved in the pathogenesis of some severe inheritable neurological disorders [115,152,188]. These so-called Cr-deficiency syndromes form a group of inborn errors [156]. Compromising either one of the two enzymes involved in endogenous Cr synthesis, i.e., AGAT or GAMT [179], or on the other hand the CRT, lead to Cr-deficiency [54] (see above and Fig. 3). In CRT deficient patients, Cr is completely lacking in the brain, as demonstrated by non-invasive proton magnetic resonance spectroscopy (MRS) [130]. Patients with Cr-deficiency syndromes clinically present with graded forms of a number of neurological deficits including speech delay, mental retardation, epileptic seizures, autism and brain atrophy, suggesting a major involvement of cerebral gray matter [164]. Due to the neurotoxic effects of GAA [211] that accumulates in the gray matter, patients suffering from GAMT deficiency also show a dystonic hyperkinetic movement dis-

order [170]. Measurement of GAA in body fluids can therefore be used to discriminate the involvement of GAMT in patients with a Cr-deficiency syndrome as they show high GAA concentration, while patients with involvement of AGAT have low and those with a disorder of the CRT normal concentrations of GAA. CRT deficient patients on the other hand show a significative elevated ratio of Cr to its major breakdown product, creatinine, in the urine. Not surprisingly, GAMT and AGAT deficiency can be treated by oral Cr supplementation [162], while patients with CRT-deficiency do not respond to this type of treatment [126,174]. However, Cr treatment in these cases has to be done on a long-range term (months or years of treatment), with very high doses of Cr required in order to see an increase in CNS Cr levels. This probably reflects the poor permeability of the BBB for Cr. Cr treatment of patients with GAMT-deficiency resulted in normalization of brain Cr and in one study also in an improvement of behavior (Table 2). These neuropathological conditions again emphasize the importance of the CK/PCr-system for the brain.

### 3.3. Hyperammonemia

Inborn errors of ammonia metabolism, such as urea cycle deficiencies and organic acidemias, can lead to Cr depletion in developing brain cells, possibly by interfering with Cr transport and synthesis pathways (for review see [46]). Interestingly, it has been shown *in vitro* that treating developing brain cells exposed to ammonium with Cr protects them from axonal growth inhibition due to ammonium exposure, which might be one of the irreversible effects of hyperammonemia on CNS development [38]. Cr supplementation to hyperammonemic neonates and children might thus represent a way to protect their developing CNS from some of the deleterious effects of ammonium.

## 4. Creatine and acute neurological disorders

### 4.1. Cerebral ischemia and stroke

Cerebral ischemia, a situation in which the brain does not receive enough blood flow to maintain normal neurological function, is known to rapidly lead to neuronal cell death due to compromised energy metabolism [120]. In line with this notion, Berger et al. could demonstrate that Cr administration protected immature hippocampal tissue from hypoxic–ischemic injury [22]. Neuroprotective effects of Cr supplementation have also been reported in animal models of ischemia [1,113]. Similarly, Cr treatment resulted in a reduction in stroke volume in mice exposed to transient focal cerebral ischemia, interestingly in absence of significant changes in brain Cr, PCr and ATP levels [139]. Hence, this observation likely indicates for a non-energy-related effect of Cr administration (see above). The authors presented in their paper some evidence that an effect of Cr on vasodilatory response in the brain might be responsible for the observed effects.

### 4.2. Traumatic brain and spinal cord injury

When the brain or the spinal cord experiences a traumatic injury, a series of cellular and molecular events in the injured tissue is initiated that leads to further damage in the surrounding area, the penumbra. This secondary damage is often larger in extent than the primary insult and is, at least in part, due to ischemia and, importantly, a compromise of cellular bioenergetics. In models of experimental brain injury, Cr-mediated neuroprotection has consequently been demonstrated [155,178]. In a prospective randomized study investigating the effects of Cr in children and adolescents suffering from traumatic brain injury, Sakellaris et al. reported that administration of Cr resulted in a significantly better clinical outcome in cognitive, personality/behavior, self-care and communication aspects in the Cr-treated group as compared to control subjects [147] (Table 2). Cr supplementation has also been shown to have moderate protective effects after spinal cord injury [84,141]. Notably the observed effects exerted by Cr were rather small. For all situations when patients experience a rapid and acute brain or spinal cord injury it seems, however, unlikely that patients would immediately benefit from Cr supplementation since exogenous Cr is taken up slowly into CNS tissue [93]. It is therefore suggested that Cr should be delivered as soon as possible after the insult directly to the sites of injury, e.g., by perfusion of the affected region or intra-cerebroventricular administration, ways that have been shown to lead to a fast increase of Cr levels in the brain [143].

### 4.3. Injury of the peripheral nerve

Not much has been published so far on the effects of Cr in situations of peripheral nerve injury. Peripheral nerve injury produces denervation of the associated muscle fibers and may be treated by microsurgical nerve repair. By means of an experimental paradigm of sciatic nerve transection in the rat, it has been reported that systemic Cr treatment of animals promoted reinnervation of the muscle and functional recovery [135]. At present and to our knowledge no clinical trials addressed the potential of Cr administration in patients suffering from peripheral nerve injury, so it remains open whether the beneficial effects observed in the animal model can be transferred to the situation in humans.

## 5. Creatine and neurodegenerative diseases

Neurodegenerative disorders are a group of acquired or inherited diseases characterized by a progressive loss of cells from one or multiple regions of the nervous system. Despite intensive research efforts to elucidate the underlying mechanisms, the etiology of neuronal cell death in most neurodegenerative diseases still remains enigmatic. However, there are a number of similarities in the fundamental biochemical processes involved in the pathogenesis and progression of these otherwise different pathological states. The concepts of energy depletion, oxidative stress by reactive oxygen species and reactive nitrogen species, excitotoxicity, and mitochondrial dysfunction have been implicated in most if not all neurodegenerative disorders [19,41]. Although these processes may be directly or indirectly involved in the pathogenesis of a given disease, they converge in final common pathways of either necrosis or apoptosis. Substantial evidence indicates that energy dysfunction plays either a primary or secondary role in cell death in neurodegenerative disorders, and even in normal aging. Mitochondria are critical organelles in the regulation of the cellular energy status. Mitochondrial dysfunction results in ATP depletion, which may contribute to neuronal cell death. Moreover, these organelles are also involved in excitotoxicity, generation of free radicals, calcium buffering, and apoptotic pathways [19]. Mitochondrial mutations, particularly at complexes I and III, can lead to generation of reactive oxygen species, and accumulation of mitochondrial DNA mutations in aging and Alzheimer's disease has been shown to be linked to oxidative stress [52,172]. These processes provide potential targets for the therapy of neurodegenerative diseases.

### 5.1. Alzheimer's disease

Alzheimer's disease (AD) is a common neurodegenerative disease leading to progressive dementia. AD is characterized by the

loss of neurons particularly of the cholinergic system and the appearance of two typical lesions in the brain known as neurofibrillary tangles and amyloid plaques. Mutations in amyloid precursor protein (APP) result in abnormal processing of APP and accumulation of beta-amyloid peptide, the main constituent of amyloid plaques in the AD brain [26]. BB-CK has been shown to be significantly inactivated by oxidation in AD patients, which may result in further compromise of the energetic state of neurons and exasperate the disease process [2]. In addition, recently discovered Cr deposits in the brain of transgenic AD mice, as well as in the hippocampus from AD patients indicate a direct link between cellular energy levels, mitochondrial function, Cr metabolism and AD [74]. Neuroprotective effects of Cr have been observed in models of AD with cultured neurons undergoing neurotoxic insults by glutamate excitotoxicity or by exposure to beta-amyloid protein [39]. Hence, it may be speculated whether Cr supplementation at an early time point of the disease may prevent or delay the course of AD-related neurodegeneration [45]. In fact, a direct connection between AD and uMt-CK was discovered by showing that uMt-CK forms a complex with APP family proteins, which affects the correct import of uMt-CK into mitochondria and thus would negatively interfere with cellular energetics [116].

### 5.2. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by progressive loss of motor neurons in the brain and spinal cord [177]. Mitochondrial and energetic defects are implicated in the pathogenesis of motor neuron degeneration in ALS [62]. A marked reduction in cerebral cortex ATP levels was detected in a mouse model of ALS well before symptom onset [42], and reduced CK activity has been reported in transgenic ALS mice [204]. Accordingly, it was found that Cr supplementation showed protective properties in mouse models of ALS [63,103,210]. In addition to the effects on cellular energy metabolism, this neuroprotection could be based on antioxidant effects exerted by Cr, given the evidence that Cr has the potential to act as a direct antioxidant against aqueous radical and reactive oxygen and nitrogen species [112] or could be due to the action of uMt-CK together with Cr in coupling mitochondrial respiration tightly to ATP synthesis, by efficient ADP cycling, and thus suppress reactive oxygen species formation in mitochondria [128]. Cr reverted the cholinergic deficit present in some forebrain areas at an intermediate stage of the disease [137]. In a follow-up study, additive neuroprotective effects of oral Cr supplementation together with a cyclooxygenase 2 inhibitor were found in the same ALS mice [104]. We could demonstrate CK immunoreactivity in a subpopulation of choline acetyltransferase (ChAT) expressing neurons in the developing [13,58] and in neurons of the ventral horn of adult human spinal cord (Fig. 4) supporting the hypothesis that Cr treatment might be beneficial in ALS or other motor neuron diseases. Despite the promising findings in experimental animal models, first clinical studies failed to show a relevant benefit of Cr treatment in ALS patients [57,166] (Table 3). However, these trials have also posed unanswered questions about the optimal dosage of Cr. It has also to be considered that Cr offers potential benefits in terms of facilitating residual muscle contractility in ALS patients [117], which should be investigated in more detail [67]. A large placebo-controlled multi-center trial is currently underway to further investigate the efficacy of Cr supplementation in ALS.

### 5.3. Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease (CMT) is a group of common hereditary disorders that is characterized by slowly progressive sensorimotor neuropathy and that can lead to life-long disability in patients. It represents a heterogeneous group of genetically distinct disorders with similar clinical presentations and a large number of responsible gene mutations [29]. In a recent study, it was shown that Cr supplementation alters muscle myosin heavy chain (MHC) composition in CMT patients undergoing resistance training and that MHC changes associated with Cr supplementation can improve muscle function [171] (Table 3).

### 5.4. Huntington's disease

Huntington's disease (HD) is an autosomal dominantly inherited neurodegenerative disorder which clinically presents with progressive choreoathetotic movements in combination with severe

**Table 3**
Creatine in clinical trials for neurodegenerative diseases

| Study | Disease state | Treatment regimen | Randomized trial | No. of subjects | Efficacy | Safety |
|---|---|---|---|---|---|---|
| Mazzini et al. [122] | ALS | 20 g/d loading for 7 d 3 g/d thereafter for 6 m | No | 28 | No benefits on decline of muscle function | Yes |
| Drory and Gross [57] | ALS | 5 g/d per day for 4 m | No | 14 | No benefits on respiratory function | n.a. |
| Groeneveld et al. [77] | ALS | 10 g/d up to 16 m | Yes | 175 | No benefit | Yes |
| Shefner et al. [166] | ALS | 20 g/d loading for 5 d 5 g/d thereafter for 6 m | Yes | 104 | No benefit | Yes |
| Smith et al. [171] | CMT | 5 g/d for 12 w | Yes | 18 | Alterations in MHC isoforms Improved muscle function | n.a. |
| Tabrizi et al. [180] | HD | 10 g/d for 12 m | No | 13 | Possible stabilization of signs | Yes |
| Verbessem et al. [191] | HD | 5 g/d for 12 m | Yes | 41 | No benefit | Yes |
| Bender et al. [20] | HD | 20 g/d loading for 5 d 6 g/d thereafter for 8–12 w | No | 20 | No benefits in UHDRS but lower brain glutamate levels | Yes |
| Tabrizi et al. [181] | HD | 10 g/d for 24 m | No | 13 | Possible stabilization in some patients | Yes |
| Hersch et al. [87] | HD | 8 g/d for 16 w | Yes | 64 | Oxidative injury marker markedly reduced | Yes |
| Bender et al. [21] | PD | 20 g/d loading for 6 d 2 g/d thereafter for 6 m 4 g/d thereafter for 18 m | Yes | 60 | Benefits in mood no effect on UPDRS | Yes |
| NINDS NET-PD [132] | PD | 10 g/d for 12 m | Yes | 134 | Found not to be futile | Yes |
| Hass et al. [83] | PD | 20 g/d loading for 5 d 5 g/d thereafter for 12 w | Yes | 20 | Benefits in resistance training | Yes |

Abbreviations: ALS: amyotrophic lateral sclerosis; CMT: Charcot-Marie-Tooth disease; d: day; HD: Huntington's disease; m: month; n.a.: not addressed; PD: Parkinson's disease; UPDRS: unified Parkinson's disease rating scale; w: weeks.

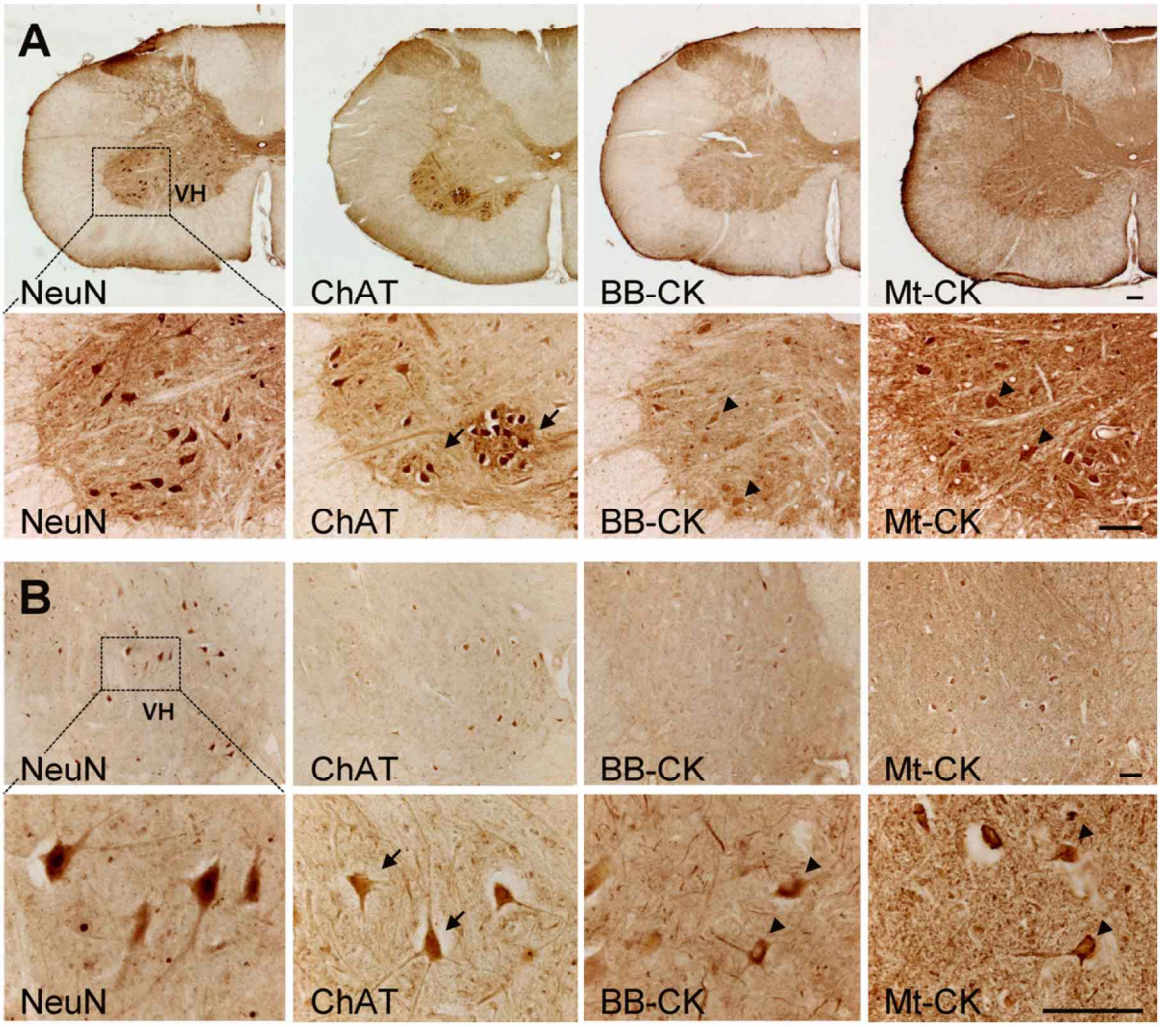


**Fig. 4.** Digitalized adjusted photomicrographs of sections from adult rat spinal cord (A) and adult human spinal cord (B) stained for the neuronal marker protein neuronal nuclei (NeuN), the cholinergic marker choline acetyltransferase (ChAT), cytosolic brain-specific creatine kinase (BB-CK) and ubiquitous mitochondrial creatine kinase (Mt-CK). The large neurons (arrows) in the ventral horn (VH) also express cytosolic brain-specific creatine kinase and ubiquitous mitochondrial creatine kinase (arrowheads) visible at higher magnifications. Scale bars: 100 μm.

cognitive and emotional dysfunction, finally leading to death [140]. HD is caused by a trinucleotide repeat expansion in the gene IT15 on chromosome 4, producing a mutant form of the Huntingtin protein (mHtt). The exact mechanism by which mHtt causes or contributes towards neuronal cell death, predominantly of striatal GABA-ergic projection neurons, remains unclear. A defect in energy metabolism has been proposed as one of the potential pathogenetic mechanisms leading to neuronal death [78]. Studies on cerebral metabolism using $^{18}$F fluorodeoxyglucose positron emission tomography (PET) showed typical patterns of diminished cerebral metabolic rates in the basal ganglia as well as in frontal and parietal regions of HD patients, correlating with the severity of the disease [85]. Recently, evidence of impaired energy metabolism in HD due to reduced mitochondrial complex II and complex III

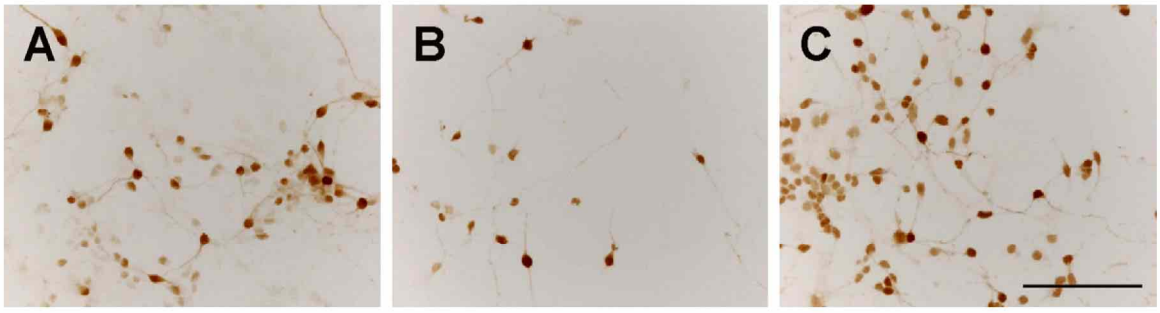


**Fig. 5.** Effects of creatine treatment on GABA-immunopositive cell densities in rat striatal cultures facing a metabolic insult. Cultures were grown for 7 days *in vitro* (DIV) and serum and glucose deprivation was performed from DIV5–7 in absence (B) or presence of creatine [5 mM] (C). Untreated cultures served as controls (A). Creatine treatment during the insult provided distinct neuroprotection for the GABA-immunopositive neurons. Scale bar: 100 μm.

activity has been reported [47,79], resulting in increased cerebral lactate levels and a reduced PCr/$P_i$ ratio in muscle. Corresponding mitochondrial defects have been described in brains from patients suffering from HD, particularly in the basal ganglia [182]. Further evidence for mitochondrial respiratory chain dysfunction has been provided by studies of transgenic mouse models of HD [183]. Increasing cellular PCr levels and thereby improving the impaired energy metabolism by exogenous Cr supplementation may therefore offer a feasible approach for reducing neuronal deterioration in HD. Using an experimental *in vitro* model of HD, we detected that Cr supplementation provided significant neuroprotection on GABA-ergic cells against glucose and serum deprivation (Fig. 5) and against 3-nitropropionic acid (3-NP) induced toxicity in striatal cultures [10]. Cr, injected intraperitoneally at 12 mg/kg body weight, was shown to protect experimental animals against convulsive behavior and lactate production elicited by intra-striatal injection of methylmalonate [145]. In addition, Cr administration increased survival, delayed motor symptoms, and significantly reduced brain lesion size in a transgenic animal model of HD [9,72] and in 3-NP exposed rats [165]. In recent clinical trials, it was reported that Cr is well tolerated and safe in HD patients [181]. Brain glutamate levels were significantly reduced after a Cr-enhanced diet [20] and serum 8-hydroxy-2′-deoxyguanosine (8OH2′dG) levels, an indicator of oxidative injury to DNA, that are markedly elevated in HD, were reduced by Cr treatment [87], indicating some efficacy of Cr treatment for this devastating neurodegenerative disease (Table 3). While at present there is no clear evidence that Cr deficiency is implicated in the pathogenesis of HD [184], MRS has demonstrated a significant decrease in the PCr/$P_i$ ratio in resting muscle in patients with HD (see above [108]). Moreover, a reduced glucose metabolism both in presymptomatic and symptomatic patients has been reported [123]. In addition, brain levels of Cr in HD patients were found to be significantly increased by 7.2% and *N*-acetylaspartate levels, a biomarker of neuroprotection, were increased by 16% as measured by MRS after Cr administration for 4 months [146]. Little, however, is known so far on the clinical benefits of Cr treatment. A recent study by Tabrizi and co-workers suggested that some patients might have been shown a benefit from Cr supplementation, as assessed by total motor score, functional capacity score or neuropsychological testing [181]. In a transgenic mouse model of spinocerebellar ataxia type 1, which is another trinucleotide repeat disease, a Cr-supplemented diet resulted in a significantly extended survival of the affected Purkinje cells, but did not prevent the ataxic phenotype [98].

### 5.5. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder presenting with the clinical symptoms of resting tremor, bradykinesia, rigidity and postural imbalance [110,111]. PD is characterized by the pathological hallmark of progressive deterioration of dopaminergic neurons in the substantia nigra, leading to a profound loss of dopaminergic input into the striatum. An impaired function of the mitochondrial electron transport system, in particular complex I, is supposed to be involved in the pathogenesis of PD [3,153,154], suggesting a mitochondrial basis for the disease. Recent research has focused on neuroprotective strategies for PD [31]. Using an experimental *in vitro* paradigm of PD, we observed neuroprotective properties of Cr against toxic insults induced by 6-hydroxydopamine (6-OHDA) [12] or 1-methyl-4-phenyl pyridinium (MPP+) [11] exposure in ventral mesencephalic rat cultures. Beneficial effects of Cr have also been demonstrated in an animal model of PD [121]. Cr supplementation in clinical pilot studies was shown to result in improved patient mood but the Unified Parkinson's disease rating scale remained unchanged [21]. A recent study showed benefits in resistance training [83], while the NINDS NET-PD trial rated Cr as found not to be futile [132] (Table 3).

## 6. Creatine and cell replacement strategies

A number of acute and chronic neurological disease states are assumed to be suitable for cell replacement therapies (for review see Goldman and Windrem [75]). The general goal of this approach is to repair the brain by replacing the neurons or glial cells lost in pathological processes. Hence, the effects of cell replacement strategies, e.g., for HD (for review see: Dunnett and Rosser [61]), PD (for review see: Dunnett et al. [60]; Lindvall and Bjorklund [119]; Paul [136]; Trzaska and Rameshwar [186]), and stroke (for review see: Bliss et al. [27]) by means of transplanting neuronal precursors or stem cells has attracted great attention. Most of our preclinical and clinical knowledge for this treatment option is at present available for PD. So it has been demonstrated that some transplanted cells show long-term survival and structural and functional integration in the host brain [14,131]. The transplanted tissue is understood to release dopamine in a regulated fashion and to reverse many of the behavioral deficits seen in animal models of PD [44,43] as well as in patients [73]. In HD, there exists a substantial body of experimental data showing the effectiveness of striatal transplants in experimental models [32,59], while preliminary studies report on motor and cognitive improvements in patients with HD neural transplantation [16,15]. In animal models of ischemic brain damage, it has been demonstrated that transplanted neuronal stem cells survive, migrate, and differentiate into appropriate neuronal phenotypes [28,102]. Furthermore, embryonic motoneurons transplanted into the axotomized tibial nerve survived and re-innervated the denervated target muscle [70]. However, at present, there are major obstacles that prevent a widespread clinical application of cell replacement approaches. These problems include typically the limited availability of donor tissue, the poor survival of transplanted cells, as well as the suboptimal innervation of the targeted structures in host brain. For example, in PD reports showed that less than 20% of the implanted cells survived the transplantation procedure [107,118]. Importantly, it was observed that most transplanted neurons died within 1 week after transplantation [18] mostly by apoptotic cell death [209]. One of the current strategies to improve cell replacement approaches, therefore, includes treatment of the cells or recipient with neuroprotective factors. In this context, factors that have the potential to improve the cellular energy metabolism, such as Cr (see above), may furthermore positively contribute to better therapeutical outcome. Wang et al. reported that forces generated during cell migration and process outgrowth require special energy demands and that guanidino kinases such as CK and arginine kinase may participate in the selective growth of growth cones [200]. Furthermore, Cr has been demonstrated to mimic the effects of the dynamin-like GTPase Drp1 on synapse density of hippocampal neurons [117]. Hence, it can be hypothesized that Cr may well support fiber outgrowth into the host brain. In addition, we have previously observed that Cr acted as a potent differentiation factor for striatal precursor neurons, inducing differentiation towards the GABA-ergic phenotype, an effect involving mitogen-activated protein kinase and phosphatidylinositol-3-kinase [10]. These data suggest that Cr may play an important role in cell fate decision during development of neuronal cells, a finding that is also supported by a report describing the expression of CK to be highly dynamic, often being transiently expressed in specific cells for a short time period only, indicating a specific function of CK during brain development [55]. Since there are many efforts on the way to find alternatives to human fetal tissue as a graft source including neuronal precursors

and stem cells, Cr holds a potential to influence the survival and differentiation of these cells.

## 7. Conclusions and outlook

While the role of Cr for the muscular system is well recognized, there is growing evidence that it also plays an important role in the normal and diseased central nervous system. This notion is based on the outcome reported for numerous experimental studies and more recently in clinical studies. The fact that elevated Cr brain levels were found after oral ingestion of Cr provides evidence that Cr can pass the BBB. Hence, potential benefits of a Cr supplementation can be expected for human patients with neurological disorders. With the limited research at present available, chronic Cr administration seems to be safe. In a pilot study on athletes, a high-dosage Cr supplementation for improving muscle strength revealed no kidney, liver or health problems [76,109]. Oral dietary supplementation, including a loading phase of 5–7 days with 4 doses of 5 g of Cr/day, followed by a maintenance dose of 2–5 g/d for 3–6 months or up to 2 years, showed an excellent safety profile [88,127]. Similarly, Cr administration at high dosage was well tolerated in premature newborns [30]. The latter observation is of particular importance for the treatment of inborn metabolic diseases. Moreover, the clinical trials summarized in Tables 1–3 did not report on adverse effects. In addition, the fact that Cr is a constituent of the regular diet and also endogenously synthesized potential benefits of Cr administration can therefore be assumed to be accomplished in absence of any major side effects. Notably, the observations with Cr supplementation in clinical trials specifically addressing effects on neurological diseases are in part disappointing as compared to the rather marked neuroprotective effects observed in corresponding animal models. At least partially, this discrepancy might be based on the fact that some of the animal models do not faithfully replicate the pathophysiology of the corresponding human disease. In addition, we assume that this may be due to unsolved questions regarding Cr dosage, schedule and time of Cr supplementation. For example, Cr doses in these animal studies were approximately 10 times higher than those used in the clinical trials. In addition, the observation of a missing neuroprotective effect of chronic Cr treatment in adult mice suffering from stroke hints to the idea that adaptive mechanisms may counteract the beneficial effects of Cr supplementation [139]. This finding asks for a better understanding of the underlying mechanisms how Cr exerts its effects and also for further considerations if Cr should be used as a long-term nutritional supplement for patients. Nevertheless, Cr remains a promising neuroprotective agent for further studies involving neurological diseases, but importantly the potential of Cr for such neuropathological conditions may only be unraveled by large multi-center studies [21]. This is supported by a recent futility clinical trial of Cr in early PD patients [132]. The clear positive effect of Cr on patient mood discovered in this trial hints strongly to the idea that such measures should be assessed in future clinical trials of patients with depressions.

Taken together, there is the need for future studies to address the mechanisms by which Cr mediates its effects and to further substantiate the potential of Cr for the treatment of neurological diseases. In this respect, the recently announced clinical trial by the National Institute of Neurological Disorders and Stroke (NINDS) aims at investigating the potential of Cr for PD. Notably, this is one of the largest clinical trials ever for PD with a total number of 1720 participants planned to be enrolled [50]. We believe that the outcome of this trial will enhance the interest in brain Cr likely sheds light on its genuine effects of Cr and Cr supplementation on brain function in health and disease. In this context it may be worth noting that recently, a major volume on "Creatine and Creatine Kinase in Health and Disease" (edited by Salomons, G.S., and Wyss, M.) has been published in: Subcellular Biochemistry Vol. 46 (2007), Springer, ISBN: 978-1-40206485-2, which may be of interest to this readership.

## Conflict of interest

There is no conflict of interest for either author.

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