Historical perspective

In 1832 the French philosopher and scientist Michel Eugene Chevreul successfully extracted creatine from meat (the muscles of mammalians) and named it "creatine" from the Greek word *κρέας* (kreas), meaning "meat". After Chevreul's discovery, Justus von Liebig, a German chemist, in 1847 demonstrated that creatine concentration was higher in wild animals compared to domestic ones and he concluded that creatine concentration in muscular tissue was dependent upon the level of activity.

In 1912, researchers at Harvard University showed that ingestion of creatine could rise muscular creatine content and later studies demonstrated that creatine supplementation induced nitrogen retention suggesting increasing protein content in muscle. This effect was reversible with the withdrawal of creatine (Haffernan, 2015).

In 1923 the content of creatine in human body was measured in about 100 grams, 95% of which stored in muscle tissue. In the light of all these findings, Alfred Chanutin, in 1926, for the first time studied the effect of creatine in humans. He administered 10 g of creatine a day for a week and found increased creatine content in muscles, proposing that creatine have anabolic effects (Chanutin, 1926).

In 1990s the use of creatine as anabolic agent to increase athletes' performance began and currently creatine is one of the most popular supplements in sport (Balsom, Söderlund and Ekblom, 1994).

In 1994, in a patient with extrapyramidal movement disorder and low creatinine concentration in serum and urine, by using proton magnetic resonance spectroscopy, a generalized depletion of creatine in the brain was described for the first time (Stöckler et al., 1994). When the Authors tried to treat the patient with arginine (a creatine precursor), they found that the metabolite guanidine acetate increased in the brain, not paralleled by an increase in creatine, indicating that the defect was in the second of the two enzymes responsible for creatine synthesis (see below).

In 2001 another patient presenting with developmental delay and hypotonia was found to have low brain creatine content: but in this case serum and urine creatine levels were increased (Salomons et al., 2001). Genetic analysis revealed a nonsense mutation in gene coding for creatine transporter and low uptake of creatine in fibroblasts coming from the patient. This was the first description of the clinical syndrome due to genetic defects of the creatine transporter.