Curative role of pantothenic acid in brain damage of gamma irradiated rats

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Abstract Radiation induced brain damage is associated with impairment of mitochondrial functions, variations in the level of neurotransmitters, and oxidative stress. Mitochondrial function is closely linked to the level of neurotransmitters since the precursors are supplied by the Krebs cycle intermediates. The objective of this study was to evaluate the influence of pantothenic acid, an essential component in the synthesis of Coenzyme A (CoA), on the activity of the Krebs cycle enzymes, isocitrate dehydrogenase (IDH), α -ketoglutarate dehydrogenase (α -KGDH), and succinate dehydrogenase (SDH); the level of aspartic, glutamic and GABA; the activity of transaminases, and oxidative stress, in the cerebrum of γ -irradiated rats. Pantothenic acid (26 mg/Kg) was orally administered to the rats, 2 h after irradiation and during the following 5 days. Animals were sacrificed the 7th day post-irradiation. The exposure of male albino rats to γ -rays (5 Gy) has triggered oxidative stress notified by a significant elevation in the level of malondialdehyde (MDA), an end product of lipid peroxidation, associated to a significant decrease in the content of phospholipids, and the antioxidant compound

glutathione (GSH). The activity of IDH, α -KGDH, and SDH, has significantly decreased, while the level of aspartic, glutamic and GABA has significantly increased. In parallel to these changes, the activity of alanine and aspartate transaminase has significantly increased, compared to their values in the control rats. Pantothenic acid treatment, has significantly attenuated oxidative stress; enhanced the activity of IDH, α -KGDH, and SDH; minimized the increase in the level of amino acids and the activity of transaminases, compared to their values in the cerebrum of irradiated rats. In conclusion, pantothenic acid could improve the level of neurotransmitters amino acids, which depends on the enzymatic activities of Krebs cycle and linked to oxidative stress.

Keywords Pantothenic acid · Gamma radiation · Brain · Krebs cycle enzymes · Transaminases · Neurotransmitters

Introduction

The increasing use of radiation technologies in medicine, industry, agriculture and in scientific researches has increased the risk for over exposure to ionizing radiation. If radiation interacts with the DNA molecule, or some other critical cellular component, it is referred to as a direct effect. Indirect effects are caused by the reaction of radiation with the water molecules that make up most of the cells volume, causing the radiolysis of water and the production of radicals which attack the critical targets. Because they are able to diffuse some distance in the cell, thus, damage from indirect action is much more common than damage from direct action [1].

The study of the effects of radiation on the nervous system is particularly difficult because of the system's own

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morphological and functional complexity, the close and intricate relationships between the nervous system and other systems of the organism and the multiplicity of endpoints whereby changes in the nervous system can be recorded. However, it has been shown that oxidative stress (excess of reactive oxygen species to antioxidants), the mitochondrial damage, and the variations in the level of neurotransmitters contribute to the radiation-induced brain injury [2, 3].

All aerobic organisms have to cope with the dangers associated with the reactive oxygen species (ROS), toxic moieties that are routinely generated as a consequence of ATP production via oxidative phosphorylation [4]. If left unchecked, ROS can damage biological macromolecules, leading to the death of the cell. Hence, all aerobic organisms possess an intricate anti oxidative defense system. Superoxide dismutase and catalase eliminate superoxide and hydrogen peroxide, respectively. Glutathione also plays a pivotal role in the detoxification of ROS. Glutathione, a tripeptide composed of L-glutamate, L-cysteine and glycine, is considered to be the most important endogenous intracellular antioxidant in mammalian cells [5]. Reduced (GSH) and oxidized (GSSG) forms of glutathione are interconvertible by the action of two enzymes, glutathione peroxidase and glutathione reductase. Alteration in the metabolism of GSH has been observed in multiple neurodegenerative diseases [6].

The Krebs cycle enzymes are essential to the survival of complex aerobic organisms and brain functions [7], such that changes in these proteins have been linked to many diseases including cancer [8, 9]. Isocitrate dehydrogenase (IDH) catalyzes the oxidative decarboxylation of isocitrate to produce α -ketoglutarate and carbon dioxide (CO_2). In eukaryotes, three isozymes have been reported IDH1 and IDH2 which are adenine dinucleotide phosphate (NADP^+)/dependent, and IDH3 is nicotinamide adenine dinucleotide (NAD^+)/dependent [10]. The IDH1 and IDH2 catalyze reversible reactions, whereas the reaction catalyzed by IDH3 is irreversible [11]. IDH1 and IDH2 mutations have recently been identified as drivers in the development of several cancers [9, 12, 13]. Alpha-ketoglutarate dehydrogenase (α -KGDH) is an enzyme complex that produces NADH directly providing electrons for the respiratory chain [14] and is a crucial target of reactive oxygen species (ROS) [15]. Its deficiency leads to brain disease [16] and many neurodegenerative disorders [17] including Alzheimer's [18] and Parkinson's disease [19]. Succinate dehydrogenase (SDH) participates in both the TCA cycle and the electron transport chain [20]. SDH catalyzes the oxidation of succinate to fumarate [21]. Reduced levels of the brain mitochondrial SDH have been linked to the progressive degeneration of nerve cells [2].

Most nerve-to-nerve signaling and all known nerve-to-muscle and nerve-to-gland signaling rely on chemical synapses at which the presynaptic neuron releases a chemical neurotransmitter that acts on the postsynaptic target cell [22]. The binding of neurotransmitters may influence postsynaptic neurons in either an inhibitory or excitatory way. Inhibitory neurotransmitters, such as serotonin, glycine, and γ -amino butyric acid (GABA), calm the brain, whereas excitatory neurotransmitters such as norepinephrine, aspartate and glutamate stimulate the brain [23]. The neurotransmitters play a major role in shaping everyday life. Their exact numbers are unknown, but more than 100 have been identified. The level of neurotransmitter can be depleted by many ways. Stress, poor diet, neurotoxins, genetic predisposition, drugs, alcohol and caffeine usage, can alter the level of neurotransmitters [24].

Amino acids are among the most abundant of all neurotransmitters present within the central nervous system [25]. Glutamate is involved in learning and memory [26]. Its excess leads to excitotoxicity and neurodegenerative diseases [27] such as Alzheimer's [28] and Parkinson's disease [29]. GABA is the major inhibitory neurotransmitter, and its concentration is 200–1000 times greater than that of the monoamines. The perturbation of the glutamatergic, and GABAergic neurotransmission, is associated with several neurological and psychiatric disorders [30]. Aspartate is an excitatory amino acid [31, 32], which excess is toxic to cortical neurons [26]. It prevents depression, attenuates schizophrenia-like symptoms [33], increase spatial memory in rats [34], and function as modulator of neurogenesis in adult [35].

Recently, evidence from human research showed that pantothenic acid (vitamin B₅) plays a pivotal role in health and brain function and its concentration in brain is 50 times higher than in plasma [36, 37]. Of particular relevance, pantothenic acid is involved in the synthesis of multiple neurotransmitters [38, 39]. Pantothenic acid is a water-soluble vitamin that derives from the Greek *pantothén*, meaning “from everywhere” due to its presence in both plant and animal foods. Excellent food sources include avocado, whole-grain cereals, legumes, eggs, meat, royal jelly, yogurt, and broccoli [40]. Adults probably require about 4–7 mg/day maintaining a whole blood level of 100–180 $\mu\text{g/dL}$, but no RDA (Required Daily Allowance) has been set [41].

The deficiency of pantothenic acid is rarely observed in humans, however, since it cannot be stored in the body and since it is absorbed in the small intestine it may be deficient in individuals suffering from intestinal damage [42]. A significant proportion of the populations of developed countries suffer from deficiencies or insufficiencies of the

B-vitamins group [37]. Pantothenic acid is readily destroyed by heat, in either alkali or acid media [43]. Previous studies concerned with radiation-induced oxidative stress in brain tissues showed that, whole body exposure of male albino rats to 5 Gy gamma radiations [44] as well as 8 Gy gamma rays given in four fractions each 7 days apart [3], provoked oxidative stress manifested by elevated lipid peroxidation and protein oxidation associated with significant decreases of antioxidants. Therefore, the objective of this study was to evaluate the influence of pantothenic acid, an essential component of coenzyme A, on oxidative stress, the activity of Krebs cycle enzymes, the activity of transaminases and the level of neurotransmitter amino acids in the brain of γ -irradiated rats.

Materials and methods

Experimental animals

Male albino rats *Sprague–Dawley* (10 ± 2 weeks old; 120 ± 10 g) purchased from the Egyptian Holding Company for Biological Products and Vaccines (Cairo, Egypt) were used as experimental animals. The animals were maintained under standard conditions of temperature, humidity and lighting with free access to standard food and drinking water ad libitum. Experimental analyses were performed in the morning at $11:00 \pm 1$ h. All animal procedures were performed in accordance with the Ethics Committee of the National Research Centre conformed to the *Guide for the care and use of Laboratory Animals* published by the National Institutes of Health (NIH publication No. 85–23, revised 1996).

Gamma irradiation

Irradiation of rats was carried out with a Canadian Gamma Cell-40 (137 Cs) (Atomic Energy of Canada Ltd, Ottawa, Ontario, Canada), at the National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt at a dose rate 0.6 rad/s. Animals were placed in a specially designed well-ventilated acrylic container and whole body irradiated with 5 Gy.

Pantothenic acid treatment

Pantothenic acid hemi-calcium salt (Sigma-Aldrich, St Louis, MO, USA) was dissolved in distilled water, and administered by gavages to the rats, at a concentration of 26 mg/kg body weight (about 3 times the daily intake) [45]. Pantothenic acid was administered to the rats, in one ml distilled water, 2 h after irradiation and continued for 5 consecutive days.

Animal groups

The animals were allocated in 4 equal groups of 5 rats each and treated in parallel. (1) Control group: normal rats receiving distilled water for 6 days; (2) pantothenic acid group: rats receiving pantothenic acid during 6 consecutive days; (3) irradiated group: whole body γ -irradiated rats with 5 Gy receiving distilled water 2 h after irradiation and for 5 consecutive days; (4) irradiated + pantothenic acid group: whole body γ -irradiated rats with 5 Gy, receiving pantothenic acid 2 h after irradiation and for 5 consecutive days.

Biochemical analysis

All chemicals and kits were obtained from Sigma-Aldrich, St Louis, MO, USA. Tissue homogenates were prepared using Teflon-glass homogenizer (Glass-Col, Terre Haute, Ind., USA). Centrifugation was performed by means of a refrigerated centrifuge (K3 Centurion Scientific Ltd, London, UK). Measurement of absorbance was done using a T60 UV/VIS spectrophotometer (PG instruments, London, UK).

Rats were sacrificed the 7th day post-irradiation by decapitation. The cerebrum was removed, kept on ice and washed with ice-cold saline. A homogenate (10% weight/volume w/v) was prepared in 0.1 M phosphate buffer (pH 7.5) containing 0.15 M KCl and was centrifuged at $1000 \times g$ for 15 min in cold centrifuge. The supernatant was stored at 4 °C until used. *Lipid peroxidation* level was assayed according to the method of Yoshioka et al. [46] based on the reaction of malondialdehyde (MDA) an end product of lipid peroxidation with thiobarbituric acid in acidic medium to yield a pink colored trimethine complex with absorption at 532 nm. The concentration of MDA was calculated as nmol/g wet wt. *Glutathione content* (GSH) was estimated according to the method of Beutler et al. [47] based on the reaction of GSH with DTNB (5,5-dithio bis 2-nitrobenzoic acid) to give a yellow colored compound with absorbance at 412 nm. The level of GSH was expressed as milligram/gram wet weight. *Phospholipids* content was determined after acid digestion of a trichloroacetic acid precipitate of protein-phospholipid as described by Connerty et al. [48]. The concentration of phospholipids was expressed as milligram/gram wet tissue.

For the determination of Krebs cycle enzyme activities the mitochondria were isolated according to Rickwood et al. [49]. The activities of NAD^+ -dependent isocitrate dehydrogenase (IDH) and α -Ketoglutarate Dehydrogenase (α -KGDH) were determined using isocitrate, and α -ketoglutarate, respectively, as the substrates, in an enzyme reaction, which results in a colorimetric product with absorbance at 450 nm (A_{450}) proportional to the enzymatic

activity present. The activity was calculated in U/g protein. One unit is the amount of enzyme that will generate 1.0 μ mole of NADH per minute at pH 8.0 at 37 °C. Succinate dehydrogenase activity was determined by generating a product with absorbance at 600 nm proportional to the enzymatic activity present and calculated in U/g protein. One unit of SDH is the amount of enzyme that generates 1.0 μ mole of 2, 6-Dichlorophenolindophenol (DCIP) per minute at pH 7.2 at 25 °C [50].

Determination of amino acids

A deproteinized tissue extract was prepared by homogenizing a portion of the cerebral hemispheres with 5% trichloroacetic acid [51]. After centrifugation (4 °C, 20 min, and 8000 g) the clear supernatant layer was decanted and washed several times with ether to remove any trace of lipids. The clean supernatant was dried and the residue washed several times with distilled water to remove any trace of ether. Then to the dried residue a suitable volume of sodium citrate buffer was added and the sample analyzed using high performance Amino Acid Analyzer, Biochem 20 (Auto Sampler Version) Pharmacia Biotech England. Data analysis of chromatogram was done by EzchemTM Chromatography Data system Tutorial and user's Guide-version 6.7 and the concentration expressed in μ g/g tissue.

The activity of transaminases was estimated using a diagnostic kit purchased from Spectrum, Egypt following the method described by Henry et al. [52].

Protein content was determined according to the method of Lowry et al. [53] using bovine serum albumin as a reference.

Statistical analysis

The data is presented as mean $\pm$ standard deviation (SD). Groups were compared by one-way analyses of variance (ANOVA), and post hoc multiple comparisons were done with LSD test using SPSS/PC software program (version 21; SPSS Inc., Chicago, IL, USA).

Results

In the current study, the administration of pantothenic acid, to normal rats, has not influenced the oxidative stress markers malondialdehyde (MDA), glutathione (GSH), and phospholipids, in the cerebrum of rats (Table 1). The activity of isocitrate dehydrogenase (IDH), α -ketoglutarate dehydrogenase (α -KGDH) and succinate dehydrogenase (SDH), in the cerebrum was in the normal level (Table 2). There was no significant change recorded for the activity of

transaminases (Table 3), and the level of the amino acids, aspartic, glutamic and GABA, when compared to their respective values in the cerebrum of control rats (Table 4).

The exposure of male albino rats to γ -rays (5 Gy) has triggered oxidative stress, demonstrated by a significant elevation in the level of malondialdehyde (MDA), with significant reduction in the content of glutathione (GSH), and phospholipids, when compared to their respective values in the cerebrum of control rats (Table 1). The activity of the Krebs cycle enzymes in mitochondria, isocitrate dehydrogenase (IDH), α -ketoglutarate dehydrogenase (α -KGDH), and succinate dehydrogenase (SDH), has significantly decreased (Table 2), while the activity of alanine and aspartate aminotransferase (ALT and AST) has significantly increased, compared to their respective control levels (Table 3). Together with these changes, a significant increase was recorded in the level of aspartic, glutamic and γ -amino butyric acid (GABA) (Table 4).

The administration of pantothenic acid to the rats, 2 h after irradiation and for 5 days, has significantly attenuated oxidative stress, enhanced the activity of IDH, α -KGDH, SDH, and diminished the increase of ALT and AST activities, as well as, the increase in the level of amino acids, in comparison to their respective values in the cerebrum of irradiated rats.

Discussion

The brain, the most metabolically active organ in the body, is particularly susceptible to oxidative damage due to the high content of easily oxidizable unsaturated fatty acids, the high content of oxygen and iron, and relative to other organs the brain is poor in antioxidants [54]. Consequently, exposure to ionizing radiation incites numerous biochemical changes [3]. In the current study, the whole body exposure of rats to γ -radiation (5 Gy) has triggered oxidative stress; reduced the activity of the Krebs cycle enzymes; increased the activity of transaminases, and elevated the level of neurotransmitter amino acids in the cerebrum. These biochemical changes might be ascribed to the interaction of free radicals with the cellular molecules. Hence, the increase of MDA associated to the decrease of phospholipids might be attributed to the interaction of hydroxyl radicals ($\cdot$ OH) with the polyunsaturated fatty acids present in the phospholipids portion of cellular membranes [55]. Also, the decrease of GSH might be linked to its interaction with free radicals leading to the formation of oxidized glutathione (GSSG) [56].

Although the elimination of ROS by antioxidants is critical to the survival of all organisms, it is also important to appreciate the role that adaptive mechanisms play to

Table 1 The influence of pantothenic acid on the level of malondialdehyde (MDA), glutathione (GSH) and phospholipids, in the cerebrum of rats, the 7th day after exposure of the whole body to γ -rays (5 Gy)

	Control	Pantothenic acid	γ -irradiated	γ -irradiated + pantothenic acid
MDA (nmol/g wet weight)	280 $\pm$ 20	272 $\pm$ 22 (−3%) ^{aNS}	357 $\pm$ 41 (+28%) ^{a**}	310 $\pm$ 40 (−11%) ^{aNS} ^{b*}
GSH (mg/g wet weight)	1.08 $\pm$ 0.17	1.12 $\pm$ 0.14 (+4%) ^{aNS}	0.77 $\pm$ 0.10 (−28%) ^{a**}	0.94 $\pm$ 0.09 (−13%) ^{aNS} ^{b*}
Phospholipids (mg/g wet weight)	3.56 $\pm$ 0.41	3.71 $\pm$ 0.14 (+4%) ^{aNS}	2.80 $\pm$ 0.22 (−21%) ^{a**}	3.15 $\pm$ 0.15 (−12%) ^{a**} ^{b*}

Pantothenic acid (26 mg/Kg body weight) was given orally to rats, 2 h post-irradiation, and for 5 consecutive days. Data are expressed as mean $\pm$ standard deviation (n = 6). The number between brackets shows the percentage of change from the respective control value

^a Significance versus control, ^b Significance versus γ -irradiated, *NS* not significant

* Significant at $p < 0.05$; ** Highly significant at $p < 0.01$

Table 2 The influence of pantothenic acid on the activity of α -ketoglutarate dehydrogenase (α -KGDH), isocitrate dehydrogenase (IDH) and succinate dehydrogenase (SDH), in terms of U/g protein, in the cerebrum (mitochondria) of rats, the 7th day after exposure of the whole body to γ -rays (5 Gy)

	Control	Pantothenic acid	γ -irradiated	γ -irradiated + pantothenic acid
IDH	400 $\pm$ 50	425 $\pm$ 35 (+6%) ^{aNS}	260 $\pm$ 34 (−35%) ^{a**}	322 $\pm$ 26 (−19%) ^{a**} ^{b**}
α -KGDH	245 $\pm$ 40	252 $\pm$ 33 (+3%) ^{aNS}	155 $\pm$ 29 (−37%) ^{a**}	202 $\pm$ 17 (−17%) ^{aNS} ^{b**}
SDH	450 $\pm$ 60	470 $\pm$ 31 (+4%) ^{aNS}	305 $\pm$ 16 (−32%) ^{a**}	370 $\pm$ 28 (−18%) ^{a**} ^{b**}

Pantothenic acid (26 mg/kg body weight) was given orally to rats, 2 h post-irradiation, and for 5 consecutive days. Data are expressed as mean $\pm$ standard deviation (n = 6). The number between brackets shows the percentage of change from the respective control value

^a Significance versus control, ^b Significance versus γ -irradiated, *NS* not significant

* Significant at $p < 0.05$; ** Highly significant at $p < 0.01$

Table 3 The influence of pantothenic acid on the activity of alanine and aspartate transaminase (ALT and AST), in terms of U/mg wet weight, in the cerebrum of rats, the 7th day after exposure of the whole body to γ -rays (5 Gy)

	Control	Pantothenic acid	γ -irradiated (5 Gy)	γ -irradiated + pantothenic acid
ALT	50 $\pm$ 6.0	51 $\pm$ 13 (+2%) ^{aNS}	70 $\pm$ 15 (+40%) ^{a**}	60 $\pm$ 14 (+20%) ^{aNS} ^{bNS}
AST	530 $\pm$ 75	540 $\pm$ 37 (+2%) ^{aNS}	665 $\pm$ 39 (+25%) ^{a**}	595 $\pm$ 19 (+12%) ^{a**} ^{b**}

Pantothenic acid (26 mg/kg body weight) was given orally to rats, 2 h post-irradiation, and for 5 consecutive days. Data are expressed as mean $\pm$ standard deviation (n = 6). The number between brackets shows the percentage of change from the respective control value

^a Significance versus control, ^b Significance versus γ -irradiated, *NS* not significant

* Significant at $p < 0.05$; ** Highly significant at $p < 0.01$

lower the production of ROS. The Krebs cycle plays an intriguing role in this regard [57]. In the current study, the inactivation of the Krebs cycle enzymes might be a dedicated effort by the cells to diminish the production of NADH and NADPH with the concomitant reduction in ROS formation. In this regard, a reduction of the IDH enzyme activities in the brain of animals exposed to

oxidative stress was reported to elicit neuroprotection [58]. Furthermore, the inhibition of α -KGDH and accumulation of α -ketoglutarate can readily nullify ROS with the concomitant formation of succinate, a moiety that may signal anaerobic metabolism [59]. In the same context, [14] reported that in the presence of a high concentration of free radicals, α -KGDH is inhibited.

Table 4 The influence of pantothenic acid on the level of amino acids, in terms of $\mu\text{g/g}$ wet weight, in the cerebrum of rats, the 7th day after exposure of the whole body to γ -rays (5 Gy)

	Control	Pantothenic acid	γ -irradiated	γ -irradiated + pantothenic acid
Aspartic acid	410 $\pm$ 67	420 $\pm$ 73 (+0.2) ^{aNS}	567 $\pm$ 69 (+38) ^{a**}	500 $\pm$ 66 (+22) ^{a*bNS}
Glutamic acid	1325 $\pm$ 262	1349 $\pm$ 332 (+1.8) ^{aNS}	1761 $\pm$ 113 (+33) ^{a**}	1462 $\pm$ 169 (+10) ^{aNSb*}
GABA	300 $\pm$ 68	290 $\pm$ 57 (3.3) ^{aNS}	450 $\pm$ 64 (+50) ^{a**}	360 $\pm$ 70 (+20) ^{aNSb*}

Pantothenic acid (26 mg/kg body weight) was given orally to rats, 2 h post-irradiation, and for 5 consecutive days. Data are expressed as mean $\pm$ SD ($n = 6$). The number between brackets shows the percentage of change from the respective control value

^a Significance versus control, ^b Significance versus γ -irradiated, NS not significant

* Significant at $p < 0.05$; ** Highly significant at $p < 0.01$

The variations in the level of neurotransmitters have been attributed to a decreased synthesis, an increased catabolism, a decreased storage in synaptic vesicles or a prevented re-uptake in synaptic vesicles. In an elegant study regarding the alterations of neurotransmitter amino acids in brain tissues, [60] showed that, acute cerebral ischaemia is not accompanied by an imbalance between excitatory and inhibitory amino acids, but by an increase in all neurotransmitter amino acids. In the current study, a significant increase was recorded in the level of glutamic and aspartic acid, as well as, in the level of GABA. The increase of glutamic and aspartic acid may be linked to the inhibition of the Krebs cycle leading to the accumulation of α -keto glutarate and oxaloacetate, which by way of the addition of an amine group by transamination give glutamate and aspartate, respectively. On the other hand, glutamate/GABA form an excitatory/inhibitory pair in the brain [23], which could explain the increase of glutamate concomitant with GABA, and raise the possibility that, in oxidative stress, an increase in the level of GABA might exert a neuroprotective role in the brain [60]. The results support that the neurotransmitters regulate each other's [61–63].

According to the European commission's report [64] the acute oral LD₅₀ values for pantothenic acid are 10,000 mg/kg in mice and rats. In the current study, the administration of pantothenic acid (26 mg/kg body weight) to normal rats during 6 consecutive days had no significant effect on oxidative stress; the activity of the Krebs cycle enzymes; the activity of transaminases, and the level of neurotransmitter amino acids in the brain, which corroborates the safety of pantothenic acid [65]. In irradiated rats, pantothenic acid treatment has significantly attenuated oxidative stress; enhanced the activity of the Krebs cycle enzymes; decreased the activity of transaminases, and reduced the level of neurotransmitter amino acids, when compared to their respective values in the irradiated rats.

The modulator role of pantothenic acid in the radiation-induced oxidative stress might be associated to its effectiveness in the scavenging of free radicals [66, 67] and the improvement of the antioxidant status [68, 69]. In this respect, pantothenic acid, by regulating the Krebs cycle activity, would contribute in the synthesis of GSH by increasing the production of NADPH [70]. Moreover, it could be postulated that the administration of pantothenic acid to rats antagonizes the radiation-induced decrease of pantothenic acid [45] caused by the radiation-induced intestinal damage [71]. Therefore, being an essential component in the synthesis of coenzyme A (CoA) [72], which in turn is involved in the transformation of pyruvate and α -ketoglutarate to acetyl-CoA and succinyl-CoA, respectively, two compounds which participate in the Krebs cycle [73, 74], pantothenic acid would contribute in the regulation of the Krebs cycle mechanism with consequent modulation of the neurotransmitter amino acids.

It could be concluded that pantothenic acid may be a useful adjunct to improve the level of neurotransmitters amino acids, which depends on the enzymatic activities of Krebs cycle and linked to oxidative stress in the cerebrum of γ -irradiated rats.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

Ethical approval All the experimental procedures were carried out according to the principles and guidelines of the Ethics Committee of the National Research Centre conformed to "Guide for the care and use of Laboratory Animals" for the use and welfare of experimental animals, published by the US National Institutes of Health (NIH publication No. 85–23, 1996).

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