Amino Acids (1997) 13: 91–103

Amino
Acids

Dietary tryptophan and aging*

Review Article

H. Sidransky

Department of Pathology,
The George Washington University Medical Center,
Washington, District of Columbia, U.S.A.

Accepted April 30, 1997

Summary. This paper considers findings which may relate to whether there may be a correlation between dietary L-tryptophan and aging. Early studies had reported that animals fed a tryptophan-deficient diet showed increased longevity compared to controls. Although decreased serotonin levels due to the tryptophan-deficient diet was considered of importance for the increased longevity, a more likely explanation was decreased diet intake due to the deficient diet. Indeed, decreased diet consumption as well as decreased energy intake have been shown to lengthen the lifespan of animals. Greater quantitative assessment between the effect of a tryptophan-deficient diet and that of decreased energy intake needs to be obtained. Our recent findings that one mouse strain ($NZBWF_1$), which is autoimmune susceptible and has a relatively short lifespan, demonstrate a significantly decreased binding affinity for L-tryptophan by hepatic nuclei when compared to other mouse strains are of much interest. These results stimulated us to reconsider the issue whether L-tryptophan itself may influence the aging process. Since L-tryptophan has a regulatory effect on hepatic protein synthesis which may be related to its binding to a specific nuclear receptor, much akin to what occurs with certain steroid hormones which are considered to be involved in the aging process, this review explores the possibility that L-tryptophan via its regulatory action may be of great importance and merits further investigation. This indispensible dietary component may have a vital regulatory control in the normal state and possibly also during the process of aging.

* This study was supported by U.S. Public Health Service Research Grant DK-45353 from the National Institute of Diabetes and Digestive and Kidney Diseases.

Keywords: Amino acids – L-tryptophan – Aging – Nuclear receptors – Liver – $NZBWF_1$ mice

For many years our laboratory ha s been concerned with the effects and actions of L-tryptophan (Sidransky, 1985). It is one of the indispensible amino acids which, more than any other amino acid, can be converted into many other substances of important biological significance. We have been concerned with the unique actions of L-tryptophan especially in relation to its regulatory effect on hepatic protein synthesis. A brief review of the significant findings of experimental studies concerned with determining the mechanism responsible for the L-tryptophan-induced (single administration) stimulation of hepatic protein synthesis follows. Tryptophan administration rapidly increases mRNA (poly(A)mRNA) in the cytoplasm of rat liver (Murty and Sidransky, 1972; Murty et al., 1976). An enhanced rate of translocation of mRNA from nuclei into the cytoplasm (demonstrated in in vivo and in vitro experiments) appears to account for this effect (Murty et al., 1977, 1979). Intracytoplasmic translocation of poly(A)-mRNA from informosomal pools is not responsible (Garrett et al., 1984). Tryptophan administration causes an enhancement in the activities of a variety of liver enzymes (Sidransky, 1985). It increases the activities of hormonally and nutritionally sensitive enzymes, many of which are not necessarily related to the metabolism of tryptophan (Ballard and Hopgood, 1973; Chee and Swick, 1976; Cikak, 1979; Kaplan and Pitot, 1970; Schimke et al., 1965). Also, tryptophan stimulates the activities of enzymes of hepatic nuclear envelopes that influence the phosphorylation and dephosphorylation processes (those considered to be involved in the regulation of nucleocytoplasmic translocation of mRNA) (Murty et al., 1983). In addition, nuclear poly(A)polymerase is stimulated (Kurl et al., 1993). L-tryptophan has been found to bind rapidly to protein of the nuclei and this binding appears to be correlated with the increased in vitro release of hepatic nuclear RNA (Sidranky et al., 1984) and with the enhanced activity of hepatic nuclear poly(A)polymerase activity (Kurl et al., 1992). Pretreatment of isolated hepatic nuclei with concanavalin A prevents the increase in binding and in nuclear RNA release, suggesting that glycoprotein(s) may be involved in the process whereby tryptophan acts (Sidransky et al., 1984). Indeed, tryptophan increases ^{14}C-glucosamine incorporation into proteins of the subcellular fractions, particularly that of nuclear membrane (Sidransky et al., 1986). Recent studies have focused on the ability of tryptophan to bind to a nuclear envelope tryptophan receptor protein (glycoprotein) (Kurl et al., 1987; 1988). This receptor has high specificity for L-tryptophan and the binding is saturable, stereospecific, and of high affinity. This tryptophan binding protein of hepatic nuclear envelopes has been purified to apparent homogeneity using either concanavalin A-agarose or tryptophan-agarose. The receptor has an M_R of 34,000 (64,000 when using several protease inhibitors) (Kurl et al., 1988). The hepatic nuclear envelope protein contains two binding components for ^{3}H-tryptophan as revealed by Scatchard analysis. One of the components has a high affinity for tryptophan (K_D 0.67 nM and B_{max} 21.3 fmol/mg protein) whereas the low affinity binder has both a higher K_D (18.1 nM) and

concentration (B_{max} 327.3 fmol/mg protein) (Kurl et al., 1987). In a study concerned with the possible association of the tryptophan receptor and poly(A)polymerase in rat hepatic nuclei, evidence was found that suggests that the tryptophan receptor protein and poly(A)polymerase share structural homology (Kurl et al., 1992). Schroder et al. (1989) have described a tryptophan binding protein of nuclear envelopes of mouse lymphoma (L5178g) cells that has similar characteristics as reported earlier in our laboratory for rat hepatic nuclear envelopes. Nuclei of other cells or tissues, including cultured murine macrophages (WLG5) (Sidransky et al., 1994), brain (Cosgrove et al., 1992), and hepatoma (H5123 and 19) (Sidransky et al., 1995), have been reported to demonstrate in vitro specific binding to L-tryptophan. Recently we reported mouse strain differences in the L-tryptophan binding affinity by hepatic nuclei (Sidransky and Verney, 1997a): $NZBWF_1$ mice had a significantly diminished in vitro binding affinity compared to that of other strains of mice (Swiss, DBA, SJLF/J and BALB/C) which had similar binding affinities to that of rats (Sprague-Dawley (Kurl et al., 1987, 1988) and Lewis (Sidransky and Verney, 1994)). It is of interest that $NZBWF_1$ mice are autoimmune-susceptible and have a relatively short life span and demonstrate many features of accelerated aging (Yunis et al., 1972). Recently, we found that $NZBWF_1$ mice, which have a significant decrease in hepatic nuclear binding affinity for L-tryptophan, also have a difference in the nuclear binding affinity for L-tryptophan between young ($6^1/_2$ weeks old) and older (30 weeks old) male $NZBWF_1$ mice (Sidransky and Verney, 1997b). Based upon several studies (Sidransky et al., 1990; Sidransky and Verney, 1996a), the affinity of nuclear tryptophan binding appears to correlate with the ability and degree of L-tryptophan-induced stimulation of hepatic protein synthesis: increased nuclear binding of tryptophan appeared to lead to a greater stimulation of hepatic protein synthesis. These findings are summarized in Table 1.

Based upon the recent findings relating to the decreased hepatic nuclear binding affinity for L-tryptophan of $NZBWF_1$ mice (Sidransky and Verney, 1997 a,b), we have focused our attention on tryptophan and aging in regard to protein metabolism. Earlier our laboratory had probed into how aging could influence aspects of hepatic protein metabolism, particularly polyribosomes in relation to protein synthesis, during fasting and starvation of rats (Sidransky and Verney, 1971) and in pregnant and lactating rats and their fetuses and pups (Sidransky and Verney, 1988). Indeed, the literature contains many studies concerned with the effects of nutrition on controls (transcriptional and translational) of protein synthesis in liver (Murty, 1985). Studies concerned with the effect of aging on hepatic protein synthesis are numerous (Cook and Beutow, 1981; Viskup et al., 1979). Generally, younger animals have higher rates of hepatic protein synthesis than do older animals.

In an earlier review article on tryptophan and its unique actions in 1985, only brief comments on tryptophan and aging were included (Sidransky, 1985). Now I decided to probe deeper into this topic and review additional reports by others as well as our own. In light of our recent knowledge

Table 1. Effects of L-tryptophan on liver of rats and mice[a]

Effect[b] (Comparison between tryptophan-treated and control groups)	Rats	Mice	
	Sprague-Dawley	Swiss	$NZBWF_1$
Enzyme activities			
Tryptophan dioxygenase	+++	+++	+++
Nuclear poly(A)polymerase			
Bound	+	+	+
Free	+	++	0
Nuclear nucleoside triphosphatase	++	++	++
Nuclear RNA efflux (^{14}C-orotate-labeled RNA release)	++	++	0
Protein synthesis (in vitro ^{14}C-leucine incorporation)	++	++	0 to +
Nuclear L-tryptophan binding			
Specific ^{3}H-tryptophan binding (basal levels)	70%	63%	34%
Age effect on levels ($6^1/_2$wk/30wk) (%)			
Specific ^{3}H-tryptophan binding		100/94	21/42

[a]Results from earlier studies (Kurl et al., 1987; 1993; Sidransky, 1985; Sidransky and Verney, 1994; Sidransky et al., 1997a; 1997b); [b]Rating of effects: 0–19%, 0; 20–49%, +; 50–100%; ++; >100%, +++.

that L-tryptophan binds to a specific nuclear receptor much akin to that of some hormones that act as modulators of protein synthesis, it seemed appropriate to focus attention on the biological behavior of nuclear receptors and to consider whether they may possibly have effects or influences on aging.

Tryptophan ingestion and longevity

Long-term ingestion of a tryptophan-deficient diet

Dietary manipulation has been considered as a possible means for altering the rate of mammalian aging. Indeed many earlier and more recent studies have demonstrated the life-extending effect of calorie restriction, whereby the rate of aging appears to become retarded (Berg, 1960; Berg and Simms, 1960; McCay, 1952; Ross, 1972). In regard to tryptophan and aging, some 21 years ago Segall and Timiras (1976) undertook experimental studies to evaluate the effect of long-term dietary tryptophan restriction on the process of aging in the rat. They related the observed state of maturational and growth arrest for long periods under their experimental conditions to the ability of the tryptophan-deficient diet to lower brain serotonin levels. Along with a slight increase in the average lifespan at late ages of the experimental animals, they observed a delay in the age of onset of visible tumors. However, their pair-fed

control rats, as well as calorie restricted rats in experimental studies reported by others (Berg, 1960; Berg and Simms, 1960; McCay, 1952; Ross, 1972), also demonstrated a prolonged lifespan and a delayed onset of tumors. Increased longevity in mice fed a low tryptophan diet has also been reported (DeMarte and Enesco, 1986). Low levels of tryptophan in the diet cause voluntary restriction of food intake (Segall and Timiras, 1976) as well as hormonal alterations (Segall, 1979). Thus, in the absence of clear quantitative assessment of findings due to a tryptophan-deficient diet from those due to decreased diet (energy) intake, it is at present difficult to attribute prolonged longevity specifically to low intake of tryptophan per se. At present it appears probable that the effect could more likely be attributed to the general response pattern of decreased ad libitum diet consumption due to the ingestion of a deficient diet (Sidransky, 1972).

Shorter-term ingestion of a tryptophan-deficient diet

Early experiments showed that tryptophan-deficiency led to a disturbance in growth in mice (Willcock and Hopkins, 1906) and rats (Osborne and Mendel, 1914). A variety of pathological changes in experimental animals have been ascribed to tryptophan deficiency: cataracts (Totter and Day, 1942), corneal vascularization (Sydenstricker et al., 1947), anemia (Albanese et al., 1943), fatty liver (Cole and Scott, 1954; Samuels et al., 1951), pancreatic atrophy (Samuels et al., 1951), and scoliosis (Poston and Rumsey, 1983).

Many biochemical changes in tissues and organs of experimental animals fed tryptophan-deficient diets have been described (Albanese et al., 1943; Samuels et al., 1957). Most studies were concerned with changes in the liver. Of interest were the differences in hepatic metabolism and pathological changes that were observed dependent upon the means of feeding (ad libitum versus force-feeding) single essential amino acid deficient diets (Sidransky, 1972; Van Pilsum et al., 1957). Date derived from such experimental studies have been summarized in an earlier review (Sidransky, 1972). Based upon an overall evaluation of our own studies (Sidransky and Verney, 1970) and those of others dealing with feeding tryptophan-deficient diets (Naito and Kandatsu, 1970; Samuels et al., 1951; Van Pilsum et al., 1957), it appears that most of the observed pathologic findings were probably related to deficiency of essential amino acids or even that of poor-quality protein rather than that specific to tryptophan deficiency.

Studies on the effects of tryptophan administration on the liver

As reviewed above, the effects of feeding for one or more days a tryptophan-deficient diet on the liver did not appear to be specific due to that type of diet deficiency itself. Therefore, our attention shifted to an interest in the effects of a single administration of L-tryptophan itself on hepatic metabolism. Here we have demonstrated unique effects attributable to L-tryptophan, many of which have been described earlier.

The metabolic changes attributable to L-tryptophan alone need to be considered in terms of possible alterations which may be influenced by or related to aging. Our findings of altered (decreased) hepatic nuclear tryptophan receptor affinity in $NZBWF_1$ mice compared to mice of other strains (Sidransky and Verney, 1997a) suggested that L-tryptophan may affect liver metabolism differently under certain conditions (especially in relation to strain). Such or similar differences in response may possibly occur with the receptors of certain hormones which play regulatory roles. For this reason, the effects of selected hormones which have receptors in hepatic nuclei and have regulatory roles are reviewed as they may relate to aging. The existence of possible interrelations of the actions of certain hormones and of L-tryptophan through their receptors may indicate modifications which occur with aging and may therefore offer intriguing possibilities. Possibly L-tryptophan, an important dietary component, may under certain circumstances influence vital metabolic functions differently such that the process of aging is altered. Further investigation into the metabolic affects and actions of L-tryptophan is needed and should reveal the true role that it may play under normal conditions and with aging.

Hepatic nuclear receptors for L-tryptophan and for certain hormones as metabolic modulators

Since L-tryptophan has been demonstrated to have a specific nuclear receptor in liver (Kurl et al., 1987, 1988), it was of interest to consider whether its receptor may be similar or related to other hepatic nuclear receptors. Triiodothyronine (T_3) receptors and glucocorticoid receptors are part of a group of nuclear proteins, "ligand responsive transcription factors", that belong to the same protein superfamily as steroid receptors (Sap et al., 1986; Weinberger et al., 1986). The steroid hormone nuclear receptors have been extensively investigated and the complexity of their actions on a vast number of physiologic and pathologic processes is apparent (Beato et al., 1995). In an attempt to determine whether the hepatic nuclear receptor for L-tryptophan may possibly be related to those hormonal receptors, some experimental studies searching for possible similarities have been conducted. Since selenite, a catalyst of the oxidation of sulfhydryl (thiol) groups, has been observed to have a significant inhibitory effect on the binding characteristics of the glucocorticoid (Tashima et al., 1989) and of the 3, 5, 3′-triiodothyronine (T_3) (Brtko and Filipcik, 1994) receptors of rat livers, we recently tested the effect of selenite on the tryptophan receptor and also observed a significant inhibitory effect on binding (Sidransky and Verney, 1996b). Since it has been considered that steroid and thyroid hormones may exert their effects through fundamentally similar mechanisms (Thompson and Evans, 1989; Weinberger et al., 1986), our above finding suggested that the nuclear L-tryptophan receptor may possibly be related to the other nuclear receptors and possible commonalities between their actions may exist. If yes, similar responses of these nuclear receptors to aging may possibly occur. Indeed, whether such speculative possibilities are true need to be investigated. Although a number

of studies have been conducted dealing with other nuclear receptors and aging, little is known about the nuclear tryptophan receptor and aging. We feel that such studies are needed. It is indeed conceivable that a nutritional component, such as L-tryptophan, and its receptor may have a regulatory role which may be influential or be altered during aging. Possibly controlled ingestion of L-tryptophan may be a means to affect the process.

Age-dependent regulation of glucocorticoid receptors in liver

Glucocorticoids exert their multitude of actions on a variety of cellular and metabolic effects. Alterations in the adaptive responsiveness to hormones are age-related as are changes in the induction of many enzymes (Kanungo, 1980). These hormone-mediated responses are controlled by binding to specific intracellular receptors. Age-related changes in the steroid receptor binding sites occur in most of animal tissues (Kalimi, 1980). Increased numbers of binding sites for glucocorticoid receptors in liver have been reported at the weanling stage compared to the mature state of Long-Evans rats (Sharma and Timiras, 1987) and for 3 month old verses 12 month old Sprague-Dawley rats (Roth, 1974). This suggests that glucocorticoid receptor level and some of its physiochemical properties differ at various ages of rats and these differences may lead to functional changes in tissue response as a function of age. Age-related changes in glucocorticoid receptors have been described in a number of organs (Kalimi et al., 1973).

Age-dependent regulation of thyroxine and triiodothyronine receptors in liver

Aging has often been defined as an altered state of tissue responsiveness to hormonal signals and/or as altered synthetic and secretory processes of the endocrine glands. Since thyroxine (T_4) and triiodothyronine (T_3) have diverse effects on metabolic processes, they may be important components of the aging process. Altered thyroid function with aging has been reported (Cole et al., 1982). Although in vitro binding of T_3 to liver nuclear receptor suggests that the density of the receptor does not change with aging (Valcana, 1979; Valcana and Timiras, 1978), alterations in receptor-controlled cellular functions could still occur with aging and may be indirectly induced through changes in availability of cellular T_4 and T_3 and, consequently in receptor saturation. Margarity et al. (1985) studied the effects of aging on the in vivo subcellular distribution and binding of T_3 and T_4 to hepatic nuclei as well as on the process of T_4 to T_3 conversion in Long-Evans rats. They observed that with aging in vivo nuclear T_3 binding did not change significantly but nuclear T_3 binding derived from T_4 was decreased as a consequence of reduced T_4 to T_3 conversion and also T_4 binding was depressed.

Strain and species differences in response to L-tryptophan

Recently we have reported that $NZBWF_1$ mice but not other strains of mice (Swiss, SJL, DBA and BALB/c) have a decreased affinity for hepatic nuclear

binding of L-tryptophan as well as a decrease in tryptophan-induced stimulation of hepatic protein synthesis (Sidransky and Verney, 1997a). It is of interest that $NZBWF_1$ mice, that are autoimmune-susceptible and have a relatively short life span (Yunis et al., 1972), have been observed to have a diminished affinity for hepatic specific binding for [^{3}H]-2,3,7,8-tetra-chlorodibenzo-p-dioxin (TCDD) as compared to that of control (C57B/6) mice (Kurl, R. N., Personal communication). Exposure to specific polychlorinated hydrocarbons, such as TCDD, produces a wide variety of species- and tissue-specific toxic and biological effects and many of these responses are mediated by the Ah receptor (Garrison et al., 1996). Whether L-tryptophan receptor binding affinity may possibly be related to that of the Ah receptor needs to be explored. Also, we have found that hamsters in contrast to guinea pigs, which act like rats and Swiss mice, demonstrate species differences in regard to L-tryptophan and liver, similar to those reported in $NZBWF_1$ mice (Sidransky and Verney, 1997b). The altered nuclear specific binding affinity in these species correlate with responses (binding or lethal toxicity) to TCDD by guinea pigs (TCDD susceptible) and hamsters (TCDD resistant) (Unkila et al., 1995). Thus, data regarding hepatic nuclear specific binding of L-tryptophan raise the possibility that a correlation between binding affinity with L-tryptophan and the effects of TCDD effects may exist (Sidransky and Verney, 1997b) and this needs further investigation.

Blood, brain and intestinal tryptophan levels and aging

Under normal conditions free plasma amino acid concentrations show relatively little variation (Felig, 1975). Yet a number of reports indicate that plasma total tryptophan levels are lower in the older than in the younger population for both sexes (Demling et al., 1996). A number of reports have indicated that serum tryptophan levels are decreased in some disease states (Fuchs et al., 1990; Sainio et al., 1996). How this developes is not clear, although a number of hypothoses have been proposed. It does indicate that under certain conditions the serum tryptophan levels are altered, the full consequences thereof are unknown.

Tang and Melethil (1995) studied the kinetics of blood-brain barrier uptake of tryptophan in rats as affected by aging and reported that aging decreases the ability of the blood-brain barrier to transport tryptophan. Navab and Winter (1988) investigated the effect of aging on intestinal absorption of tryptophan in vitro in the rat. Using whole-thickness everted jejunal rings to measure L-tryptophan uptake they observed that it was reduced in older (2 year old) rats compared with that in younger (1/2 year old) rats.

The above observations deal with the consequences of aging on tryptophan levels in different components or areas of the body. Whether and how these changes in levels of tryptophan may in themselves influence the process of aging is not clear.

Concluding remarks

The rational for exploring whether specific amino acids may play a role in influencing the process of aging is a justifiable one. Altered expression of genes must indeed influence longevity. Studies and hypotheses for amino-acid-dependent regulation of gene expression in mammalian cells have been reported (Kilberg et al., 1994). It is vital to gain a definition of the molecular steps whereby the cellular concentration of individual amino acids can regulate gene expression and this will contribute to our understanding of metabolic control in mammalian cells during the lifetime of the host.

This review has attempted to consider whether and how L-tryptophan may play a role in aging. Although the current evidence does not answer the posed question, it does offer suggestions that L-tryptophan could be involved. In order to attempt to understand how this indispensible and unique amino acid may act, it is vital to learn about its important regulatory effects. This review focused special attention on L-tryptophan's ability to bind to a specific hepatic nuclear receptor, which is somewhat similar to that which occurs with a number of steroid hormones. Based upon our earlier findings we speculated that the nuclear tryptophan receptor protein may be involved in gene regulation (Kurl et al., 1988), possibly in a manner similar to that demonstrated for several steroid receptors which regulate gene transcription (Kaufmann et al., 1986; Lefebore and Novosad, 1980; Simmer et al., 1984). Our recent finding that $NZBWF_1$ mice have a significantly diminished nuclear tryptophan receptor affinity in liver in comparison to that of other mouse strains is of great interest (Sidransky and Verney, 1997a). $NZBWF_1$ mice are autoimmune-susceptible and have a relatively short life span with many features of accelerated aging (Yunis et al., 1972). In $NZBWF_1$ mice the decreased nuclear receptor affinity for L-tryptophan in liver appeared to be diminished even more in young ($6^1/_2$ week old) than in older (30 week old) mice (Sidransky and Verney, 1997b). An explanation for the latter finding is not clear, but possibly represents some minor adaptation in the 30 week old mice over that in the $6^1/_2$ week old mice. Nonetheless, both age groups of $NZBWF_1$ mice clearly have significantly less nuclear tryptophan receptor affinity than that in Swiss mice.

At the present time no definitive evidence exists that L-tryptophan per se is involved in the process of aging. The early reports that animals fed a tryptophan-deficient diet had an increase in longevity should most likely be attributed to decreased diet intake. In this paper the unique effects of L-tryptophan on hepatic protein synthesis which is related to a regulatory effect of L-tryptophan related to a specific nuclear (envelope) receptor for this amino acid are reviewed. Since some similarities between the specific nuclear receptor for L-tryptophan and the nuclear receptors for steroid hormones appear to exist, it is appropriate to speculate that under some circumstances L-tryptophan may possibly act like steroid hormones which have been demonstrated to play roles in the aging process. Such speculation is mainly designed to stimulate and encourage further investigation concerning how L-tryptophan acts as a regulatory control of protein metabolism

in the liver and probably also in other organs in the normal state. Such information may then be used to determine whether L-tryptophan has a role in aging.

A full understanding as to how L-tryptophan acts in animals and in humans, although still unresolved, is of critical importance. The outbreak in 1989 of a new disease, the eosinophilia-myalgia syndrome, which implicated L-tryptophan manufactured by a Japanese supplier (Belongia et al., 1992; Sidransky, 1994) has raised new questions as to how L-tryptophan itself, even without impurities or contaminants, may affect a number of organs. New and additional understanding of how L-tryptophan affects humans, normally and during aging, is essential. Conceivably, this unique amino acid, especially in light of its action on nuclear membrane receptors, may prove to have an important role in and during the process of aging.

References

Albanese AA, Holt Jr LE, Kajdi CN, Frankston JE (1943) Observations on tryptophane deficiency in rats. Chemical and morphological changes in the blood. J Biol Chem 148: 299–309

Ballard FJ, Hopgood MF (1973) Phosphopyruvate carboxylase induction by L-tryptophan: effects on synthesis and degradation of the enzyme. Biochem J 136: 259–264

Beato M, Herrlech P, Schutz G (1995) Steriod hormone receptors: many actors in search of a plot. Cell 83: 851–857

Belongia EA, Mayeno AN, Osterholm MT (1992) The eosinophilia-myalgia syndrome and tryptophan. Annu Rev Nutr 12: 235–256

Berg BN (1960) Nutrition and longevity in the rat. I. Food intake in relation to size, health and fertility. J Nutr 71: 242–254

Berg BN, Simms HS (1960) Nutrition and longevity in the rat. II. Longevity and onset of disease with different levels of food intake. J Nutr 71: 255–263

Brtko J, Filipcik P (1994) Effect of selenite and selenate on rat liver nuclear 3,5,3′-triiodothyronine (T_3) receptor. Biol Trace Elem Res 41: 191–199

Chee PY, Swick RW (1976) Effect of dietary protein and tryptophan on the turnover of rat liver ornithine aminotransferase. J Biol Chem 251: 1029–1034

Cihak A (1979) L-tryptophan action on hepatic RNA synthesis and enzyme induction. Mol Cell Biochem 24: 131–142

Cole AS, Scott PP (1954) Tissue changes in the adult tryptophan-deficient rat. Br J Nutr 8: 125–138

Cole GM, Segall PE, Timiras PS (1982) Hormones during aging. In: Vernadaker A, Timiras PS, (eds) Hormones in development and aging. SP Medica and Scientific Books, New York, pp 477–550

Cook JR, Beutow DE (1981) Decreased protein synthesis by polysomes, tRNA and aminoacyls-tRNA synthetases isolated from senescent rat liver. Mech Ageing Dev 17: 41–52

Cosgrove JW, Verney E, Schwartz AM, Sidransky H (1992) Tryptophan binding to nuclei of rat brain. Exp Mol Pathol 57: 180–192

DeMarte ML, Enesco HE (1986) Influence of low tryptophan diet on survival and organ growth in mice. Mech Ageing Dev 36: 161–171

Demling J, Langer K, Mehr MQ (1996) Age dependence of large neural amino acid levels in plasma. Focus on tryptophan. Adv Exp Med Biol 398: 579–582

Felig P (1975) Amino acid metabolism in man. Annu Rev Biochem 44: 933–955

Fuchs D, Foreman A, Hagberg L, et al (1990) Immune activation and decreased tryptophan in patients with HIV-1 infection. J Interferon Res 10: 599–603

Garrett CT, Cairns V, Murty CN (1984) Effect of tryptophan on informosomal and polyribosome associated messenger RNA in rat liver. J Nutr 114: 50–57

Garrison PM, Tulles K, Aarls JMMJ, et al (1996) Species-specific recombinant cell lines as bioassay systems for the detection of 2,3,7,8-tetrachloridibenzo-p-dioxin-like chemicals. Fundamental Appl Toxicol 30: 194–203

Kalimi M (1984) Glucocorticoid receptors: from development to aging. Mech Ageing Dev 24: 129–138

Kalimi M, Beato M, Feigelson P (1973) Interaction of glucocorticoids with rat liver nuclei. I. Role of the cytosol protein. Biochemistry 12: 3365–3371

Kanungo MS (1980) Biochemistry of ageing: changes in enzymes during ageing. Academic Press, London, pp 79–126

Kaplan JH, Pitot HC (1970) The regulation of intermediary amino acid metabolism in animal tissues. In: Munro HN (ed) Mammalian protein metabolism, vol 4. Academic Press, New York, pp 387–443

Kaufmann SH, Okret S, Wikstrom AC, et al (1986) Binding of the glucocorticoid receptor to the rat liver nuclear matrix. The role of disulfide bond formation. J Biol Chem 261: 11962–11967

Kilberg MS, Hutson RG, Laine RO (1994) Amino acid-regulated gene expression in eukaryotic cells. FASEB J 8: 13–19

Kurl RN, Verney E, Sidransky H (1987) Tryptophan binding sites on nuclear envelopes of rat liver. Nutr Rep Int 36: 669–677

Kurl RN, Verney E, Sidransky H (1988) Identification and immunohistochemical localization of a tryptophan binding protein in nuclear envelopes of rat liver. Arch Biochem Biophys 265: 286–293

Kurl RN, Barsoum AL, Sidransky H (1992) Association of poly(A)polymerase with tryptophan receptor in rat hepatic nuclei. J Nutr Biochem 3: 366–372

Kurl RN, Verney E, Sidransky H (1993) Effect of tryptophan on rat hepatic nuclear poly(A)polymerase activity. Amino Acids 5: 263–271

Lefebore YA, Novosad Z (1980) Binding of androgens to a nuclear-envelope fraction from the rat ventral prostate. Biochem J 186: 641–647

Margarity M, Valcana T, Timiras PS (1985) Thyroxine diiodination, cytoplasmic distribution and nuclear binding of thyroxine and diiodothyronine in liver and brain of young and old rats. Mech Ageing Dev 29: 181–189

McCay CM (1952) Chemical aspects of aging and the effect of diet upon aging. In: Liansing AI (ed) Cowdry's problems of ageing, 3rd edn. Williams & Wilkins, Baltimore, p 139

Murty CN (1985) Effects of nutrition on transcriptional and translational controls of protein synthesis in liver. In: Sidransky H (ed) Nutritional pathology, pathobiochemistry of dietary imbalances. Dekker, New York, pp 63–113

Murty CN, Sidransky H (1972) The effect of tryptophan on messenger RNA of the liver of fasted mice. Biochim Biophys Acta 262: 328–335

Murty CN, Verney E, Sidransky H (1976) Effect of tryptophan on polyriboadenylic acid and polyadenylic acid-messenger ribonucleic acid in rat liver. Lab Invest 34: 77–85

Murty CN, Verney E, Sidransky H (1977) The effect of tryptophan on nucleocytoplasmic translocation of RNA in rat liver. Biochim Biophys Acta 747: 117–128

Murty CN, Verney E, Sidransky H (1979) In vivo and in vitro studies on the effects of tryptophan on translocation of RNA from nuclei on rat liver. Biochem Med 22: 98–109

Murty CN, Hornseth R, Verney E, Sidransky H (1983) Effect of tryptophan on enzymes and proteins of hepatic nuclear envelopes of rats. Lab Invest 48: 256–262

Naito H, Kandatsu M (1970) Effect of essential amino acid-deficiency on protein nutrition. Part III. Incorporation of ^{35}S-methionine into the tissues of rats fed on tryptophan-deficiency. Agric Biol Chem 34: 1078–1083

Navab F, Winter CG (1988) Effect of aging on intestinal absorption of aromatic amino acids in vitro in the rat. Am J Physiol 254: 6631–6636
Osborne TB, Mendel LB (1914) Amino acids in nutrition and growth. J Biol Chem 17: 325–349
Poston HA, Rumsey GL (1983) Factors affecting dietary requirement and deficiency signs of L-tryptophan in rainbow trout. J Nutr 113: 2568–2577
Ross MH (1972) Length of life and caloric intake. Am J Clin Nutr 25: 834–838
Roth GS (1974) Age-related changes in specific glucocorticoid binding by steroid-responsive tissues of rats. Endocrinology 94: 82–90
Sainio EL, Pulkki K, Young SN (1996) L-tryptophan: biomedical, nutritional and pharmacological aspects. Amino Acids 10: 21–47
Samuels LT, Goldthorpe HC, Dougherty TF (1951) Metabolic effects of specific amino acid deficiencies. Fed Proc 10: 393
Sap J, Munoz A, Damm K, Goldberg Y, et al (1986) The C-erb-A protein is a high affinity receptor for thyroid hormone. Nature 324: 635–640
Schimke RT, Sweeney EW, Berlin CM (1965) The roles of synthesis and degradation in the control of rat liver tryptophan pyrrolase. J Biol Chem 240: 322–331
Schroder HC, Wenger R, Gerner H, et al (1989) Suppression of the modulatory effects of the antileukemic and anti-human immunodeficiency virus compound avarol on gene expression by tryptophan. Cancer Res 49: 2069–2076
Segall PE (1979) Interrelations of dietary and hormonal effects in aging. Mech Ageing Dev 9: 515–525
Segall PE, Timiras PS (1976) Patho-physiologic findings after chronic tryptophan deficiency in rats. A model for delayed growth and aging. Mech Ageing Dev 5: 109–124
Sharma R, Timiras PS (1987) Age-dependent regulation of glucocorticoid receptors in the liver of male rats. Biochim Biophys Acta 930: 237–243
Sidransky H (1972) Chemical and cellular pathology of experimental acute amino acid deficiency. Meth Achievm Exp Path 6: 1–24
Sidransky H (1985) Tryptophan, unique action by an essential amino acid. In: Sidransky H (ed) Nutritional pathology. Pathobiochemistry of dietary imbalances. Dekker, New York, pp 1–62
Sidransky H (1994) Eosinophilia-myalgia syndrome: a recent syndrome serving as an alert to new diseases ahead. Mod Pathol 7: 806–810
Sidransky H, Verney E (1970) Enhanced hepatic protein synthesis in rats force-fed a tryptophan-devoid diet. Proc Soc Exp Biol Med 135: 618–622
Sidransky H, Verney E (1971) Alterations in hepatic polyribosomes after fasting as a function of age. Nutr Rep Inter 3: 389–394
Sidransky H, Verney E (1988) Effect of tryptophan on livers of pregnant and lactating rats and their fetuses and pups. Proc Soc Exp Biol Med 187: 309–314
Sidransky H, Verney E (1994) Comparative studies on tryptophan binding to hepatic nuclear envelopes in Sprague-Dawley and Lewis rats. Am J Physiol 36: R502–R507
Sidransky H, Verney E (1996a) Influence of L-alanine on effects induced by L-tryptophan on rat liver. J Nutr Biochem 7: 200–206
Sidransky H, Verney E (1996b) The presence of thiols in the hepatic nuclear binding site for L-tryptophan: studies with selenite. Nutr Res 16: 1023–1034
Sidransky H, Verney E (1997a) Differences in tryptophan binding to hepatic nuclei of $NZBWF_1$ and Swiss mice: insight into mechanism of tryptophan's effects. J Nutr 127: 270–275
Sidransky H, Verney E (1997b) L-tryptophan binding to hepatic nuclei: age and species differences. Amino Acids 12: 77–84
Sidransky H, Murty CN, Verney E (1984) Nutritional control of protein synthesis. Studies relating to tryptophan-induced stimulation of nucleocytoplasmic translocation of mRNA in rat liver. Am J Pathol 117: 298–309

Sidransky H, Murty CN, Verney E (1986) Evidence for the role of glycosylation of proteins in the tryptophan-induced stimulation of nucleocytoplasmic translocation of mRNA in rat liver. Lab Invest 54: 93–99

Sidransky H, Verney E, Kurl RN (1990) Comparison of effects of L-tryptophan and a tryptophan analog, D, L-β-(1-naphthyl)alanine on processes relating to hepatic protein synthesis in rats. J Nutr 120: 1157–1162

Sidransky H, Verney E, Cosgrove JW, et al (1994) Studies with 1,1′ ethylidenebis (tryptophan); a contaminant associated with L-tryptophan implicated in the eosinophilia-myalgia syndrome. Toxicol Appl Pharmacol 126: 108–113

Sidransky H, Kurl RN, Holmes SC, Verney E (1995) Tryptophan binding to nuclei of rat liver and hepatoma. J Nutr Biochem 6: 73–79

Simmer RCM, Means AR, Clark JH (1984) Estrogen modulation of nuclear-associated steroid hormone binding. Endocrinology 115: 1197–1202

Sydenstricker VP, Hall WK, Bowles LL, Schmidt Jr HL (1947) The corneal vascularization resulting from deficiencies of amino acids in the rat. J Nutr 34: 481–490

Tang JP, Melethil S (1995) Effect of aging on the kinetics of blood-brain barrier uptake of tryptophan in rats. Pharm Res 12: 1085–1091

Tashima Y, Terui M, Itoh H, et al (1989) Effect of selenite on glucocorticoid receptor. J Biochim 105: 358–361

Thompson CC, Evans RM (1989) Transactivation by thyroid hormone receptors: functional parallels with steroid hormone receptors. Proc Natl Acad Sci 86: 3494–3498

Totter JR, Day PL (1942) Cataract and other ocular changes resulting from tryptophane deficiency. J Nutr 24: 159–166

Unkila M, Ruotsalainen M, Pohjanvvirta R, et al (1995) Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on tryptophan and glucose homostasis in the most TCDD-susceptible and the most TCDD-resistent species, guinea pigs and hamsters. Arch Toxicol 69: 677–683

Valcana T (1979) The role of triiodothyronine in brain development. In: Meisami E, Brazier MAB (eds) Neural growth and differentiation. Raven Press, New York, pp 39–58

Valcana T, Timiras PS (1978) Nuclear triodothyronine receptors in the developing brain. Mol Cell Endocrinol 11: 31–41

Van Pilsum JF, Speyer JF, Samuels LT (1957) Essential amino acid deficiency and enzyme activity. Arch Biochem 68: 42–53

Viskup RN, Baker M, Holbrook JP, Penneall R (1979) Age-associated changes in activities of rat hepatocytes. I. Protein synthesis. Exp Aging Res 5: 487–496

Weinberger C, Thompson CC, Ong ES, Lebo R, et al (1986) The c-erb-A gene encodes a thyroid hormone receptor. Nature 324: 641–646

Willcock EG, Hopkins FG (1906) The importance of individual amino acids in metabolism. Observations on the effect of adding tryptophane to a dietary in which zein is the sole nitrogenous constituent. J Physiol 35: 88–102

Yunis EJ, Teague PO, Stutman O, Good RA (1972) The thymus, autoimmunity and the involution of the lymphoid system. In: Sigel MM (ed) Tolerance autoimmunity, and aging. CC Thomas, Springfied, pp 62–119

Author's address: H. Sidransky, M.D., Department of Pathology, Ross 502, George Washington University Medical Center, 2300 Eye Street, N.W., Washington, DC 20037, U.S.A.

Received April 2, 1997