Nutrition-dependent GABA deficiencies in endocrine pancreas causes cancer, as shown for betel nut consumers and for diets de-activating vitamin B\textsubscript{6}

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Abstract

Introduction

We earlier proposed, via a published hypothesis, that deficient cellular interactions in endocrine pancreas causes cancer. These deficient interactions result from a perturbed gamma-aminobutyric acid (GABA) release by beta cells that are unable to inhibit neighbouring alpha and delta cells. Consequently, a hybrid catabolic–anabolic metabolism, mediated by glucagon and insulin, takes place. The catabolic and anabolic hormones act via kinases and phosphatases on specific enzymatic switches, thus rewiring metabolic pathways and giving mitotic cells a special advantage, leading to cancer. The pancreatic GABA starter hypothesis for cancer seems verified on a large population of regular consumers of palm tree betel nuts. These nuts contain classical GABA inhibitors that affect pancreatic mechanisms; epidemiological studies on large populations of betel nut consumers have shown that they are at an increased risk for cancer. Because vitamin B\textsubscript{6} is a cofactor of glutamate decarboxylase, GABA synthesis should decrease in processes de-activating vitamin B\textsubscript{6} thereby increasing the risk for cancer. Gyromitrin, a hydrazine found in a consumed mushroom (Gyromitra esculenta), forms vitamin B\textsubscript{6}-hydrazones; these de-activate the vitamin. Gyromitrin is carcinogenic in rodents. Pathologies de-activating vitamin B\textsubscript{6} include pellagra, a niacin deficiency due to maize diet; there, amines form adducts with vitamin B\textsubscript{6} and may increase the risk for cancer. Another adduct is a vitamin B\textsubscript{6}–pyrrole compound found in Prolinemia type II. Thus, for the carcinogenic pyrrolizidines present in Boraginaceae and other plant families, pyroles resulting from the degradation of pyrrolizidines form a pyrrole-vitamin B\textsubscript{6} adduct, which explains their carcinogenicity. This is applicable to other pyrrole-containing drugs and to diseases with pyrroluria. Moreover, vitamin B\textsubscript{6} supplementation seems to prevent cancer.

Conclusion

The aim of this review is to discuss how nutrition-dependent GABA deficiencies in endocrine pancreas could cause cancer in betel nut consumers and in those on diets with low vitamin B\textsubscript{6}.

Introduction

Areca catechu is a palm tree that produces betel nuts, which have been consumed in Asia, including India, by millions of people for centuries. Among the alkaloids found in betel nuts, arecoline, the most abundant, is a nicotinic acid ester and a cholinergic agonist. Other nicotinic acid alkaloids include arecaidine, guvacoline, guvacine and nipecotic acid, which inhibit gamma-aminobutyric acid (GABA) transporters. In addition, these alkaloids seem to bind to GABA A receptors, resulting in competition with GABA\textsubscript{1}.

It is to be recalled that GABA transporters are driven by the concentration of GABA. If cytosolic GABA levels are elevated, transporters release GABA in the extracellular space and take it up when GABA levels decrease in the cell, terminating the transmitter action\textsuperscript{2}. In endocrine pancreas, beta cells that release insulin switch off the alpha and delta cells, containing glucagon and somatostatin, respectively, with GABA. At rest, GABA is constantly released by beta cells, by the transporters, and poured over the alpha and delta cells, acting on GABA A receptors. An influx of Cl\textsuperscript{−} through these receptors hyperpolarizes alpha and delta cells, which keeps the glucagon and somatostatin release silent. Beta cells sense glycaemia via K\textsuperscript{+} channels (K\textsubscript{ATP}), which are inhibited by ATP. Hypoglycaemia decreases cellular ATP and opens these channels; the resulting K\textsuperscript{+} efflux hyperpolarizes beta cells and GABA is retained. Because the alpha cells are no longer inundated by GABA, they consequently release glucagon in response to hypoglycaemia. If nipecotic acid blocks the inward GABA transport, then the immediate effect involves an increase in extracellular GABA levels; however, in the long run, the resting efflux of GABA declines, as the poor recovery of extracellular GABA tends to deplete the GABA cell content. The blockade of alpha and delta cells by beta cells becomes gradually less efficient. Glucagon and somatostatin are then released even when insulin secretion operates\textsuperscript{2,3}. A hybrid mixed metabolism gradually takes over; it associates glucagon-mediated effects, mobilizing body stores via catabolic hormones, and insulin actions that mediate anabolism, particularly in mitotic cells that renew tissues. This metabolic situation is supposed to be carcinogenic.
as proposed by us in a recent review entitled 'A possible primary cause of cancer: deficient cellular interactions in endocrine pancreas'[^3]. Unfortunately, this hypothesis seems to be validated on millions of people in Asia, including India; these people have been consuming betel nuts for centuries. Indeed, recent epidemiological studies show that cancer risk is greater for betel nuts consumers[^4][5]. Cancers of the mouth and digestive tract, as well as the liver, or breast cancers are more frequent[^6]. Fortunately, betel nuts are often consumed with leaves of another plant—a climbing vine, piper betel (not to be confused with betel nut palm tree). Piper betel leaves have anticancer properties owing to the presence of antioxidant and anti-inflammatory compounds—eugenol, hydroxychavicol and alpha to copherol. In addition, betel nut eaters live in countries where rice is a major diet and rice is particularly rich in GABA, perhaps protecting the betel nut consumers against cancer?

The fact that betel nut consumers have more cancers seems to validate the 'grandeur nature' postulated by the hypothesis—the metabolic rewiring found in cancer starts with a pancreatic deficiency in which beta cells become unable to control alpha and delta cells.

In addition, vitamin B₆ pyridoxaldehyde, which is a cofactor of glutamate decarboxylase (GAD), forms inactive adducts with a variety of amines, which decreases the synthesis and release of GABA from beta cells and suppresses the inhibition of alpha and delta cells, thus aggravating the carcinogenic process[^1] (Figure 1).

**Discussion**

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees.

![Figure 1: Carcinogenic betel nuts affect pancreatic GABA as does diets that de-activate vitamin B₆. Many people consume betel nuts; these contain arecaidine, guvacine and nipecotic acid which block GABA interactions in endocrine pancreas. Beta cells release insulin, but their GABA release gradually gets exhausted, thereby failing to inhibit alpha and delta cells, releasing glucagon and somatostatin, respectively. The hypothesis, which considers that cancer results from this deficient GABA interaction in pancreas, seems validated by epidemiological works on large populations of betel nut consumers.](image)

[^1]: Israël M. Nutrition-dependent GABA deficiencies in endocrine pancreas causes cancer, as shown for betel nut consumers and for diets de-activating vitamin B₆. OA Cancer 2013 May 01;1(1):2.
committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Maize: The fear of cancer after the curse of pellagra

Glyphosate (roundup) is an inhibitor of 5-enolpyruvyl-shikimate-3-phosphate synthase (EPSPS). This enzyme initiates the synthesis of aromatic amino acids (tyrosine, phenylalanine and tryptophan) in plants and bacteria. A mutant EPSPH enzyme, which is resistant to glyphosate, has been discovered in Agrobacterium tumefaciens. The mutant EPSPS gene of agrobacterium was subsequently used for producing transgenic maize tolerant to glyphosate and cultivated in conditions that eliminate undesired weed sensitive to glyphosate7,8.

In nature, A. tumefaciens is attracted by wounded plants and injects a strand of its plasmidic DNA expressing the mutant EPSPS gene and other genes in the plant. The bacterial genes are incorporated into the plant genome and control the synthesis of tryptophan and derivatives leading to auxin, a plant growth hormone. Auxin elicits local tumour calllosities in the infected plant. In the callosity, the secretions of various cytokines (octopine and nopaline) that are arginine derivatives are beneficial to the bacteria9.

One may expect that transgenic maize expressing the bacterial EPSPS enzyme displays an active tryptophan biosynthesis, as this enzyme initiates the pathway leading from tryptophan to auxin in agrobacterium. Unfortunately, in maize (transgenic or wild-type), very little tryptophan is left for another pathway, leading to the synthesis of nicotinic acid (niacin). In maize, most tryptophans rather produce indolic derivatives and indolamines, which are poor niacin precursors. In animals and humans fed essentially on a maize diet, low tryptophan content of maize causes niacin deficiency, leading to a severe disease known as pellagra. This disease killed thousands of people along the Mississippi river and then in Europe, in the Landes, when maize was introduced. Joseph Goldeberger (1874–1929) discovered that pellagra was a deficiency disease, a disease of poverty, affecting populations essentially eating maize. We now know that pellagra results from a poor tryptophan conversion into niacin, also named vitamin B₆, or vitamin PP for pellagra preventis (Figure 1). Pellagra became more frequent when maize was directly milled, rather than treated, like native cultivators had empirically discovered. Native cultivators cooked maize first in alkaline solutions (initially ashes) and then in calcium hydroxide; this procedure was named nixtamalization (from an Aztec word)10. It is believed that this procedure releases bound niacin11,12 or other anti-pellagrogenic substances, such as vitamin B₂ from indolamine adducts. Indeed, tryptophan is an essential amino acid for animals; it forms niacin in the liver and then NAD⁺. One of the key enzymes synthesizing NAD⁺ is inhibited by leucine, and this effect is cancelled by vitamin B₆, which then protects from leucine-induced pellagra13 (Figure 1). In maize, indolamines probably react with the aldehyde radical of vitamin B₆ and de-activate this vitamin; this is also true for some drugs producing hydrazines with vitamin B₂. We know, for example, that patients treated with isoniazid (a nicotinic anti- tuberculosus drug) have to take much more vitamin B² to prevent symptoms recalling pellagra14. The indolamine-vitamin B₆ reaction is relevant for transgenic maize, as the bacterial gene orient the biosynthesis of aromatic amino acids from tryptophan towards indolic amines instead of niacin. The indolamines and other tryptophan derivatives de-activate vitamin B₆, forming amine-aldehyde adducts, which are perhaps disassociated in alkaline conditions. Thus, when maize is the major diet, niacin (vitamin PP) deficiency is associated with a deficiency of vitamin B₆; these deficiencies are attenuated if maize is nixtamalized. The undesired consequence of this additional vitamin B₆ loss is the inhibition of decarboxylases, such as GAD, requiring vitamin B₆. The synthesis of GABA should then decrease in relation to this intrinsic property of maize—at least when maize becomes the major diet. Moreover, it has been observed that glyphosate itself alters GABA ergic neurons15.

A maize diet leads to pellagra provoked by niacin deficiency; an associated vitamin B₆ loss should also elicit neurological troubles, dementia or epilepsy, as GABA is a major transmitter in the central nervous system. This effect may be exacerbated by drugs such as glyphosate, which interferes with glutamate/aspartate processes, thereby inhibiting GAD. In principle, a lower pancreatic GABA synthesis resulting from vitamin B₆ deficiency is possible; this would elicit a hybrid anabolism/catabolism, which may cause cancer16. This finding is in agreement with epidemiological observations on vitamin B₆ deficiencies and cancer17. However, if the maize diet is dangerous, pellagra is the initial danger, associated with niacin deficiency; an associated B₆ loss would produce, via GAD, neurological troubles, dementia or Alzheimer’s, before being ‘in fine’ carcinogenic, as recently suspected18. The properties of glyphosate that would be accidentally absorbed deserve more studies; it elicits an increased glycaemia in fishes19, suggesting a pancreatic effect and a possible pancreatic GABA deficiency. On the other hand, glyphosate may have, in addition to its interesting anti-weed effects, insecticide properties, affecting glutamatergic transmission of insect neuromuscular synapses.

Specific metabolic properties of maize led native cultivators to treat

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maize with an alkaline procedure that protected them from pellagra. We indeed know that niacin was the missing vitamin and pellagra has disappeared. If the tumourigenic effects of maize (transgenic or wild-type) were confirmed\textsuperscript{17}, it would indicate that a maize diet adds up to the known niacin deficiency, a B\textsubscript{6} deficiency acting on pancreatic mechanisms that can lead to cancer. These deficiencies appear when maize becomes the major diet—they result from intrinsic properties of maize metabolism, exacerbated if maize is uncooked or not supplemented with missing vitamins.

**Pyrroluria-associated diseases**

In line with the aforementioned description, we should mention several pathologies in which vitamin B\textsubscript{6} losses associated with pyrroluria are occasionally observed (schizophrenia, Down’s syndrome, haemolytic diseases and familial pyrroluria). An increased degradation of biological constituents into pyroles favours their reaction with vitamin B\textsubscript{6} and Zn\textsuperscript{2+}, a complex is excreted in urine. Pyrroluria was discovered on urine chromatograms of patients as ‘a mauve spot’ or kryptopyrrole, stained with Erlich’s reagent\textsuperscript{18}. The formation of aldehyde adducts with amines is in fact a general process touching other aldehydes as betaine aldehyde, and they react with ethanolamine and form lipofuscin precipitates in macular degenerative disease or Alzheimer’s disease. In case of pyridoxal-adding reactions, the resulting B\textsubscript{6} deficiency affects enzymes such as GAD, which require B\textsubscript{6} as a result, the synthesis of GABA decreases; transaminases and other enzymes are also perturbed. In general, neurological consequences predominate, convulsions and schizophrenic disorders. However, it is possible that a chronic B\textsubscript{6} deficiency may also affect enzymes in the periphery, leading to poor GABA synthesis in the pancreas. Moreover, a parallel loss of Zn\textsuperscript{2+}, excreted with the complex, impairs the physiology of beta cells; they release Zn\textsuperscript{2+} in parallel to GABA, and the loss of Zn\textsuperscript{2+} affects inhibitory controls of beta cells over neighbouring cells, inducing a possible carcinogenic process\textsuperscript{3}.

We also know that several vegetal families rich in pyrrolizidine alkaloids are tumourigenic; the pyrrolizidines are degraded into pyroles that bind to vitamin B\textsubscript{6}; this is discussed in the next section\textsuperscript{20–22}.

**Carcinogenic pyrrolizidine alkaloids**

There are other known carcinogenic alkaloids, such as pyrrolizidines, essentially found in Boraginaceae, but they are also found in some Asteraceae or Fabaceae families. Crotalaria, for example, can contaminate maize crops\textsuperscript{20} Further, *Senecio jacobaea, Symphytum officinale or Senecio riddellii* alkaloids are dangerous. Pyrrolizidine alkaloids are characterized by the necine ring (resembling a double pyrroline), and their catabolism forms pyroles\textsuperscript{21,22} that are excreted in bile or urine. They may again bind vitamin B\textsubscript{6} and change the pancreatic physiology of GABA, leading to the development of cancer in the long run. Much work remains to be done on pyrrolizidine carcinogenicity as some plants containing these compounds are consumed and/or contaminate crops. The carcinogenic mechanism for pyrrolizidine alkaloids may depend on vitamin B\textsubscript{6} loss, following the formation of adducts as observed for pyrroluria. However, this remains to be proven in this particular case. One even wonders if the same mechanism would not be valid for nicotine carcinogenicity; a catabolic derivative of the pyrrolidine ring of nicotine may be oxidized into a pyrrole, which would then bind vitamin B\textsubscript{6} and affect pancreatic GABA, leading to cancer. Alternatively, nicotine, a known cholinergic agonist, may also act as a GABA antagonist. The deactivation of vitamin B\textsubscript{6} by pyroles differs from the Schiff base or hydrazone de-activations. This special pyrrole vitamin B\textsubscript{6} adduct has been identified in a rare inherited disorder—hyperprolinemia type II—due to the lack of delta-pyrrolidine-5-carboxylate dehydrogenase. The lack of this enzyme results in the upstream accumulation of pyrrolidine-5-carboxylic acid and its reduced pyrrolidine derivative, proline, which gets elevated in the blood. It is the C4 carbon of the oxidized pyrrolidine-5-carboxylic acid that forms a covalent link with the carbonyl of vitamin B\textsubscript{6}; this new pyrrole-B\textsubscript{6} adduct is well characterized, giving another process for deactivating vitamin B\textsubscript{6}; this explains the carcinogenicity of alkaloids degraded into pyroles.

**Tumourigenicy of Gyromitra esculenta: Vitamin B\textsubscript{6}-deactivation of GABA synthesis**

Gyromita mushrooms contain a toxin named gyromitrin, a hydrazine derivative that forms hydrazones with vitamin B\textsubscript{6}, as mentioned above for isoniazide, an anti-tuberculosis drug. Acute intoxication results in convulsions, liver injury and death\textsuperscript{24,25}. When low doses of this toxin were injected into rodents, they resulted in liver carcinomas and adenocarcinomas\textsuperscript{26}. The deactivation of vitamin B\textsubscript{6} by gyromitrin elicits a decrease of GABA synthesis, causing convulsions. At lower doses, metabolic effect of hyperglycemias followed by hypoglycaemia indicate an alteration of pancreatic controls. In agreement with the hypothesis discussed, a decrease of pancreatic GABA caused cancer in these animal experiments. The carcinogenicity of gyromitrin in humans has not been observed; boiling probably decreases the level of hydrazines in gyromitra mushrooms. These mushrooms are consumed in Finland, northern Europe and North America; they should however be considered dangerous, particularly if residual gyromitrin causes a gradual deactivation of vitamin B\textsubscript{6} and a pancreatic GABA failure, leading...
It is certainly difficult to explain, at the mechanistic level, the carcinogenic effect resulting from a failure of cellular interactions mediated by GABA. However, it is quite probable that this pancreatic deficiency boosts the MAPK mitogenic route (the target of most oncogenes) and provokes cancer as for other oncogenes. We know, for instance, that GABA inhibits adrenal medulla cells. Thus, a decrease of GABA synthesis or release increases epinephrine release. Epinephrine inhibits pancreatic delta cells and does the job for GABA, which is deficient. Thus, epinephrine decreases somatostatin release from delta cells and increases the actions of growth hormone and Insulin like growth factor (IGF)\(^6\). We know that IGF activates the tyrosine kinase receptors and boosts the action of insulin, triggering the mitogenic MAPK pathway. Moreover, beta cells are known to release cholineretic derivatives controlling methylation processes; the methylation of a phosphatase PP2A targets it over the signalling kinases, where it acts as a brake, limiting the mitogenic signal. We have earlier indicated that a poor PP2A methylation boosts the MAPK pathway\(^7,28\). If beta cells release insulin without the partner compounds regulating its effect, the process may be carcinogenic the GABA is fundamental; however, Zn\(^{2+}\) and cholineretic derivatives are also essential as previously discussed. In addition, epigenetic changes induced by the hybrid metabolic situation decrease the expression of many genes. A decrease in IGFBP (an IGF binding protein), will no longer limit the action of IGF\(^7,28\). The MAPK mitogenic route is not only stimulated but is also out of control, as it occurs for other oncogenes, explaining the carcinogenicity resulting from a pancreatic beta cell deficiency. It is not insulin but its other beta cell partners that fail. We also point that GPCRs activated by the epinephrine increase ‘cross-talk’ with tyrosine kinase receptors\(^7\) and boost the MAPK route of target cells.

There is however an apparent contradiction, because some studies indicate that the direct action of GABA on some cells favours their proliferation\(^29\). This takes place, for example, in immature neurons with an elevated intracellular Cl\(^{-}\) concentration; in such cells, the action of GABA elicits an efflux of Cl\(^{-}\) by GABA A receptors, thereby depolarizing them. The depolarization opens Ca\(^{2+}\) channels and calcium activates RAS and the MAPK pathway, eliciting cell proliferation. In this case, a decrease in GABA levels would then inhibit cell proliferation. However, the situation is completely different for many more cells that are hyperpolarized by GABA. In alpha cells, for example, a decrease in GABA levels elicits a relative depolarization, increasing intracellular calcium, which triggers the release of glucagon in response to hypoglycaemia. In other target cells where GABA has a similar hyperpolarizing effect, an arrest of GABA elicits their depolarization, and a calcium increase, which activates RAS and boosts the MAPK pathway, which triggers their proliferation (Figure 2).

Inevitable mutations will select the most aggressive mitotic cells; each daughter cell inherits tyrosine kinase receptors and a mitotic capability; an increase of the IGF/IGFBP ratio plays a critical a role in this symmetrical mitosis, geometrically increasing the tumour mass\(^30\).

Conclusion

Food agencies and epidemiological studies have warned consumers of the dangers of betel nuts, tobacco, pyrrolizidine alkaloids or mycotoxins and gyromitrin. It is however difficult to avoid all potential risks; even some type of honey contains pyrrolizidines, when bees pollinate flowers containing this alkaloid. Many comestible mushrooms also contain to cancer, as observed in the animal models.

Carcinogenic effects associated with beta cell GABA deficiency

Normally, insulin and growth factors activate the mitogen-activated protein kinase (MAPK) mitogenic route and the PI3 kinase-PKB pathway via tyrosine kinase receptors. The latter will act on ‘switch board’ kinases and phosphatases, controlling enzymes supporting anabolism. In parallel, beta cells turn off alpha cells releasing glucagon with GABA; G protein-coupled receptors (GPCRs) and PKAs are switched off, while enzymes supporting catabolism are silenced. Hence, if GABA is not released, glucagon is liberated in parallel to insulin, leading to a mixed hybrid anabolism–catabolism reaction, which is typical of cancer. In the present work, we evaluated the pancreatic hypothesis, considering that deficient cellular interactions mediated by GABA cause cancer. Epidemiological works and experimental observations on vitamin B\(_{6}\)-related GABA deficiencies seem to confirm this view. It was advanced essentially because it explained the hybrid cancer metabolism, giving mitotic cells a selective advantage\(^27,28\). In fact, this hypothesis deals with deficient cellular interactions mediated by GABA; it also takes into account the fact that other insulin partners such as Zn\(^{2+}\) or cholineretic derivatives may also fail. These insulin partners are normally released for controlling neighbouring cells; they also regulate the strength of insulin signals. The hypothesis is not contradicted if GABA has positive effects on cell proliferation; this is a parallel question that deserves discussion. The action of GABA on cell proliferation has been reviewed in Ref. No. 29.
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Figure 2: Pancreatic GABA failure and proliferation. Decrease of GABA release from pancreatic beta cells has multiple causes, some of which result from vitamin B<sub>6</sub> deactivation; the decrease of GABA has several consequences. First, adrenal medulla cells are no longer inhibited by GABA and release epinephrine, which inhibits delta cells and the release of somatostatin. Epinephrine does the job for GABA. Decrease of somatostatin enhances growth hormone release, and therefore IGF, which cooperates with insulin, and strongly stimulates the tyrosine kinase receptor. The MAPK pathway is boosted; in parallel, PI3 kinase-PKB supports anabolism. Activation of the MAPK pathway induces proliferation, particularly if its normal control brakes (methylated PP2A or IGFBP) are not activated. The beta cell deficiency touches GABA, Zn<sup>2+</sup> and choline derivatives, possibly affecting PP2A methylation. Second, GABA is spilled over alpha and other cells; they are at rest, hyperpolarized by the influx of Cl<sup>-</sup> by GABA A receptors. Now, if GABA decreases, relative depolarization takes place and Ca<sup>2+</sup> entry elicits the release of glucagon from alpha cells; in other cells with similar GABA A receptors, depolarization following the arrest of GABA increases Ca<sup>2+</sup> and activates directly RAS, which boosts the MAPK oncogenic pathway even more. Third, we have seen that GABA failure elicits epinephrine release, which may activate GPCRs, inducing a transactivation of the tyrosine kinase receptor-MAPK pathway in the cells. Moreover, GPCR of the G type activates adenylate cyclase cAMP and PKA, supporting the catabolic part of this hybrid metabolism. The MAPK pathway is not only boosted but is also out of control, explaining the carcinogenicity resulting from this pancreatic beta cell failure.

Nutrition-dependent GABA deficiencies in endocrine pancreas causes cancer, as shown for betel nuts is a tradition touching millions of people in Asia, and it is difficult to change cultural habits. G. esculenta is consumed in northern countries, and cooking, probably, neutralizes the toxin. We are aware that betel nuts impair GABA release and uptake. We have identified at least three types of vitamin B<sub>6</sub> deactivations (amines hydrazines and pyroles) that decrease GABA synthesis, as vitamin B<sub>6</sub> is the cofactor of the GABA synthesizing enzymes. In all cases, the risk for cancer was clear or probable. A chronic inhibition of GABA receptors should also be carcinogenic, as observed for fipronil, a phenyl pyrazole insecticide that inhibits GABA-gated chloride channels<sup>30</sup>. When fipronil was administered to rats in their diet, for nearly 2 years, an increased incidence of thyroid gland tumours was observed. The carcinogenicity for humans has not been observed, but the risk is considered as indicated by official agencies<sup>31</sup>.

It is perhaps useful to understand carcinogenic mechanisms to neutralize them and to add protective compounds to the diet—vitamin B<sub>6</sub> or nutrients containing GABA—and avoid diets that are limited to a single nutrient. Even rice is responsible for a severe vitamin B<sub>1</sub> deficiency, Beriberi, when it is decorticated because the vitamin is present in the husk. Maize (transgenic or wild-type) is certainly dangerous when it is in the major diet; vitamin B<sub>3</sub> and B<sub>6</sub> deficiencies result from intrinsic properties of maize metabolism, and in the past, native cultivators reduced the danger associated with maize by nixtamalization.

As for the hypothesis, considering that cancer is caused by deficient cellular interactions in endocrine pancreas, resulting essentially from GABA failure, a ‘grandeur nature’ validation is unfortunately observed in populations regularly consuming betel nuts, which affect pancreatic GABA and increase the risk for cancer. There are many nutritional conditions that affect hydrazine alkaloids. Consuming betel nuts is a tradition touching millions of people in Asia, and it is difficult to change cultural habits. G. esculenta is consumed in northern countries, and cooking, probably, neutralizes the toxin. We are aware that betel nuts impair GABA release and uptake. We have identified at least three types of vitamin B<sub>6</sub> deactivations (amines hydrazines and pyroles) that decrease GABA synthesis, as vitamin B<sub>6</sub> is the cofactor of the GABA synthesizing enzymes. In all cases, the risk for cancer was clear or probable. A chronic inhibition of GABA receptors should also be carcinogenic, as observed for fipronil, a phenyl pyrazole insecticide that inhibits GABA-gated chloride channels<sup>30</sup>. When fipronil was administered to rats in their diet, for nearly 2 years, an increased incidence of thyroid gland tumours was observed. The carcinogenicity for humans has not been observed, but the risk is considered as indicated by official agencies<sup>31</sup>.

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the pancreatic system such as inadequate maize diets poor in niacin and vitamin B₆ and drugs or endogenous metabolites that decrease vitamin B₆ and pancreatic GABA. Gyromitrin poisoning, for example, has been responsible for causing cancer in animal experiments. An excess of amines and pyrroles are also dangerous. Blockade of GABA receptors is also a risk. Most of the nutritional conditions examined that disrupted this pancreatic GABAergic control system were associated with cancer, in agreement with the hypothesis. Niacin suppressed pellagra and vitamin B₁ suppressed Beriberi. We hope that controlling vitamin B₁ and GAD will decrease the risk for cancer.

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Abbreviations list
EPSPS, 5-enolpyruvyl-shikimate-3-phosphate synthase; GABA, gamma-amino butyric acid; GAD, glutamate decarboxylase; GPCR, G protein-coupled receptor; KATP, K⁺ channels inhibited by ATP; MAPK, mitogen-activated protein kinase

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