Hypertensive crisis in a patient on MAOI antidepressants following a meal of beef liver

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Certain foods[1, 2] and medications[3] may contain amines that can cause vasoconstriction and consequently a rise of blood pressure. Normally this poses no threat to the individual since the body is endowed with efficient enzyme systems for rapidly destroying these potentially hazardous substances; the principal enzymes involved are the monoamine oxidases. However, individuals ingesting the monoamine oxidase inhibitor (MAOI) class of antidepressant drugs are bereft of this protection and must avoid taking certain drugs and foods. Blackwell *et al.*[1] have suggested that foods containing p-tyramine may be particularly dangerous. They point out that cheese, certain red wines and yeast extracts are unusually rich in p-tyramine and this may cause hypertensive crises in patients on MAOI.

In the report which follows we describe how on one occasion cooked beef liver rich in p-tyramine produced the symptoms of a hypertensive crisis in a patient taking the MAOI phenelzine.

The patient concerned, a man aged 30, had suffered for many years from a chronic neurosis characterized by sexual impotence, anxiety, loss of confidence and lack of initiative. It was ultimately discovered that his neurotic symptoms responded well to the MAOI phenelzine, 20 to 40 mg. per day. The responses observed previously to tricyclic antidepressants, anxiolytic drugs, testosterone and supportive psychotherapy were unsatisfactory. Whenever the phenelzine was discontinued, the patient might remain free of symptoms for a few weeks but ultimately his difficulties would return. Before February 10, 1969, he had been taking phenelzine in this semi-continuous fashion for over two years without any adverse effects. He was intelligent and had a good understanding of the hazards of this drug.

On February 10, 1969, he had an evening meal of beef liver, bacon, mashed potatoes and turnips. He also ate a salad made from cabbage and carrots, to which had been added one teaspoonful of cole-slaw dressing. He finished his meal with a cup of tea and had no dessert. His own words can be quoted: "After supper, heart pounding rather hard. I felt it was just because I had had a big supper but it kept up and continued strong enough when I went in the car over to the drug store to get my new supply of pills. On the way back the pounding got worse and made me feel uncomfortable. As it got worse it started to go up into my head and I felt that each time my heart beat it went into my head, and it got so bad I was screaming. I could feel the veins in my neck throbbing and my whole head was going to explode. My wife took my pulse and it was pretty strong at 60 per minute."

The patient went to bed that night and in the morning the bulk of his symptoms had disappeared. When examined 48 hours after the episode his blood pressure was 110/70 and there was no evidence of neurological damage. The patient was naturally apprehensive about his experience.

On questioning, further information was elicited. The liver he had eaten had been purchased eight days before it was cooked, and had been stored meanwhile in an unfrozen state in a refrigerator. The patient had eaten liver on previous occasions during the past two years without ill effects. Not all the liver which had been cooked on February 10 had been eaten; some still remained in the refrigerator.

Laboratory investigations

When a piece of this liver was obtained from the patient, it was still cold from the refrigerator. It was immediately frozen, packed in dry ice and shipped by air from Toronto to the laboratory in Saskatoon where it was transferred to a freezer.

A sample (5 g.) was mixed in 50 ml. distilled water using a disintegrator and then homogenized to a paste. This paste was then allowed to stand for half an hour at 60° C. After cooling and centrifugation, the supernatant was percolated through an ion exchange resin (Bio-Rad, AG50W-X2, H^+ form). After washing sequentially with water, aqueous sodium acetate and water according to the procedure described by Kakimoto and Armstrong[4] the phenolic amines were eluted in alcoholic ammonia and rotary-evaporated to dryness. After trituration in 70% ethanol, aliquots were separated in various chromatographic solvent systems. A substance isographic with p-tyramine was located on paper chromatograms following separation in butanol:acetic acid:water,

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4:1:1 (v/v) and isopropylether: methyl elthyl ketone:acetic acid: water, 9:1:5:5: (v/v) and visualization with ninhydrin and diazotized spray reagents.[5] The identity of the unknown was further confirmed as p-tyramine on the basis of its forming a yellow fluorophore with 1-nitroso-2-naphthol reagent[6] on paper chromatograms following separation in the above two solvent systems. By photodensitometric scanning of the paper strips this latter technique allowed a precise quantitative evaluation: the p-tyramine concentration was 274 μg. per g. Absolute identification of the unknown was finally obtained by elution of the p-tyramine zone from a preparative, single-dimension, thin-layer chromatogram, conversion to the fluorescent 1-dimethylaminonaphthalene - 5 - sulphonyl (DNS) derivative followed by the demonstration that the formed DNS derivative was completely isographic with crystalline DNS p-tyramine in several different thin-layer chromatographic systems.[7]

The p-tyramine content of beef liver purchased locally was not high—fresh liver contained 5.4 μg. per g.—and was not increased by cooking. Liver stored in the frozen state for eight days contained 4.8 μg. per g. and this level did not rise on cooking. Liver only loosely packaged and stored in the refrigerator for eight days contained 9.5 μg. per g.; this somewhat higher value was not affected by cooking.

The tyramine might have increased as a result of the decarboxylation of tyrosine by micro-organisms, but only *Staphylococcus epidermidis* was isolated from the liver purchased in Toronto, and the ability to decarboxylate tyrosine has not been attributed to this organism. After growth in nutrient broth (Oxoid) supplemented with tyrosine, cells were harvested, washed and subsequently incubated with radioactive tyrosine,[8] but no labelled tyramine could be demonstrated in the incubate following ion exchange and paper chromatography.

Staphylococcus epidermidis is commonly found on skin, and contamination could have arisen subsequent to the cooking process. The bacteria most likely to have produced the very high tyramine content of the liver are species of streptococci,[9] but the cooking process would have been lethal to micro-organisms and, unfortunately, a sample of raw liver was not available for analysis. Attempts to implicate a pre-cooking streptococcal contamination by analyzing a sample for the sugar rhamnose, a characteristic cell wall constituent, using the technique described by Cummins and Harris,[10] was not successful.

Using the fluorimetric analytical technique described by Udenfriend,[11] no measurable amount of tryptamine could be found in any of the liver samples. It is of interest, however, that on the original paper chromatograms used to separate tyramine a substance with an R_f value similar to histamine was seen. Although a positive identification was not attempted, subsequent paper chromatographic separations indicated that this substance was isographic with synthetic histamine and exhibited the correct coloured zones with the various spray reagents including the o-phthalaldehyde fluorophore.[12] Semi-quantitative visual estimations suggested a "histamine" concentration of 65 μg. per g. in the liver from Toronto and 50 μg. per g. in various livers obtained in Saskatoon.

Discussion

This is the second occasion that we know of in which the ingestion of liver has produced hypertensive symptoms in the presence of chronic MAOI administration. Hedberg, Gordon and Glueck[13] describe how, following a single meal of chicken livers in a psychiatric hospital, six patients on tranylcypromine developed hypertensive reactions. Like us, they were able to obtain a sample of the meal and found that the suspected livers were rich in p-tyramine. They reported approximately 100 μg. per g.; this is about one-third of the value reported here. They were unable to find appreciable quantities of p-tyramine in chicken livers from other sources.

The origin of the high p-tyramine content in the liver from Toronto is not at present understood. It is a well-known fact that several types of streptococci could cause this by decarboxylation of the amino acid tyrosine of which there is a plentiful supply in liver, but attempts to demonstrate such contamination by direct and indirect means were not successful. The *Staphylococcus epidermidis* which was isolated is apparently unable to perform this decarboxylation. It is quite possible that autolytic processes were responsible, but attempts to reproduce them in Saskatoon were unsuccessful.

Our data indicate that patients ingesting MAOI should be warned not only of the dangers of consuming foods rich in p-tyramine and other amines and their precursers but also of the dangers of some foods which may give rise to high amine levels as a result of bacterial contamination and/or ageing processes. Unfortunately, only too often one recognizes spoiled foods in retrospect rather than at the time they are presented for consumption. It is apparent that more needs to be known about the amine contents of natural, prepared and spoiled foods.

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