Effects of *Fusarium moniliforme* and Corn Associated with Equine Leukoencephalomalacia on Rat Neurotransmitters and Metabolites (43089)

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Abstract. ***Fusarium moniliforme*** **(FM) is associated with equine leukoencephalomalacia (ELEM) and hepatotoxicities in horses and rats. The neurochemical effects of ELEM-associated corn naturally infected with FM and FM strain MRC 826 were studied in rats. Increases in brain 5-hydroxyindoleacetic acid (5-HIAA, major metabolite of serotonin, 5-HT) and 5-HIAA/5-HT ratios were observed in rats fed the ELEM-FM corn. These rats had reduced body weights (17%, $P < 0.01$) and increased brain weight/body weight ratios (14%, $P < 0.01$) as compared with controls that were fed commercial corn. Rats fed a rodent chow supplemented (16%, w/w) with corn cultures of FM (MRC 826) had brain 5-HT and 5-HIAA increased (11% and 60%, $P < 0.01$, respectively). At 20% FM (MRC 826)-chow diet, the 5-HIAA levels were increased (18%, $P < 0.01$). In both the 16% and 20% diets, brain 5-HIAA/5-HT ratios were increased (45%, $P < 0.01$ and 10%, $P < 0.05$), body weights reduced (30% and 18%, $P < 0.01$) and brain weight/body weight ratios increased (40% and 16%, $P < 0.01$), respectively. The incidences of microscopic liver lesions (particularly bile duct proliferations, hepatocellular hyperplasia, and focal necrosis) were consistent with rats fed the FM contaminated and FM-fortified diets. These results suggest a possible FM (ELEM-associated)-induced dysfunction in either 5-HT metabolism or 5-HIAA elimination in rat brains.** [P.S.E.B.M. 1990, Vol 194]

Equine leukoencephlomalacia (ELEM), a disease characterized by liquefactive necrosis of the brain, is associated with *Fusarium moniliforme* (FM)-contaminated corn and FM (MRC 826) corn cultures (1–4). The onset of the disease is usually sudden with ataxia, paresis, apathy, hypersensitivity, and frenzy (5). Fumonisin B_1 and B_2 have been isolated from FM cultures (strain MRC 826) (6) and experimental evidence indicates that fumonisin B_1 causes ELEM (7). The neurotoxic signs induced by the FM toxin(s) may reflect dysfunction in neurotransmitter metabolism prior to its gross manifestations. The detection of primary dysfunction in neurotransmitter synthesis, storage, release, and/or turnover prior to necrosis would be valuable. The objective of these experiments was to determine the neurochemical effects in rats of ELEM-associated corn screenings naturally contaminated with FM and FM (MRC 826) cultured on corn.

Received July 26, 1989. [P.S.E.B.M. 1990, Vol 194]
Accepted March 5, 1990.

0037-9727/90/1943-0265$2.00/0

Materials and Methods

Animals. Male Sprague-Dawley rats (Harlan Industries Inc., Indianapolis, IN), 4–5 weeks of age, were acclimated for approximately 14 days on a rodent chow diet (Agway, Ins., Waverley, NY) housed individually in wire mesh stainless steel cages equipped with automatic waste water flush systems; photoperiod was 12-hr light/12-hr dark with temperature controlled at 22°C. Water and feed were provided *ad libitum* for 4 weeks. Animals were weighed initially and at weekly intervals. Food consumption was measured weekly and animals were observed daily for toxic signs.

Diet Preparation and Fungal Culture. *Experiment 1.* Corn screenings (CS-1 and CS-2) naturally contaminated with *F. moniliforme* (8, 9) and associated with separate cases of ELEM (CS-1; Dr. S. Kasten, Illinois Department of Agriculture, Centralia, IL; CS-2, Dr. F. Galey, University of Illinois, Urbana, IL) were fed using a white dent seed corn (Trucker's Favorite) as the control (8–10). Analyses of the corn screenings for common mycotoxins revealed no aflatoxins or trichothecenes (8, 9); however, zearalenone was detected in both CS-1 (approximately 0.3 $\mu g/g$) and CS-2 (approximately 0.8 $\mu g/g$) (8–10). Analyses of CS-1 and CS-2 for chlorinated hydrocarbons or organophosphates revealed < 0.01 $\mu g/g$ whereas the control corn contained approximately 0.07 $\mu g/g$ methoxychlor. There were no detectable concentrations of lead (<1 $\mu g/g$) or mercury (<0.5 $\mu g/g$) in any of the corn diets. Infection of *F. moniliforme* in CS-1 and CS-2 was determined in 15 samples. Kernels of the subsamples were rinsed with sterile water and then with 5.25% sodium hypochlorite (5 min each). Five milliliters of each rinsing was plated on potato dextrose agar medium (Difco Co., Detroit, MI), incubated at 26°C for 2 to 4 weeks, and the number of *F. moniliforme* colonies determined. CS-1 produced *F. moniliforme* colonies from water rinsings (10^6 colonies/kernel) and the corn kernels (98%). CS-2 produced *F. moniliforme* colonies only from the hypochlorite-treated kernals (95%). Therefore, CS-1 was internally and externally infected whereas CS-2 was only internally infected.

Experiments 2 and 3. Fusarium moniliforme (MRC 826), obtained from W. F. O. Marasas, Medical Research Council, Tygerburg, Republic of South Africa, was used to inoculate the corn which was cultured for 4 weeks as described (11). In Experiment 2, a white dent variety (Trucker's Favorite, as above) was the medium placed in 2.8-liter Fernback flasks with an equal volume of water (1 kg corn/liter of H_2O). In Experiment 3, a yellow variety (Reid's Yellow Dent) was used as the medium following placement in carboys (7–10 lb of corn/carboy) with 40% moisture. The cultured corn was freeze dried, ground in a Wiley Mill, and added to basal rat chow at either 16% (Experiment 2) or 5% and 20% (Experiment 3). In addition, autoclaved-ground corn was added to the 5% FM diet so that the concentration of corn was 20% (w/w). Basal rat chow was the control diet in Experiment 2. Two control diets were designed for Experiment 3: (i) autoclaved-ground corn added to basal rat chow (20% w/w) and (ii) pelletted rodent chow used to substantiate Experiment 2. The diets were stored at −18°C in plastic-lined metal containers. The three procedures were: Experiment 1—CS-1, CS-2 versus corn (n = 5/group); Experiment 2—16% FM (MRC 826) (n = 12) versus rat chow (n = 8); and Experiment 3—20% FM (MRC 826) and 5% FM (MRC 826) vs 20% corn and rat chow (n = 15/group).

Fumonisins Assay. Fumonisin B_1 and B_2 (6) were quantitated in CS-1, CS-2 (R. D. Plattner, personal communication), and the FM cultures (12). Fumonisin B_1 was 132 and 14 $\mu g/g$ in CS-1 and CS-2, respectively. In Experiment 3, the 20% FM diet had 139 and 131 $\mu g/g$ Fumonisins B_1 and B_2, respectively. In Experiment 2, all of the MRC 826 culture material was used in diet preparation so fumonisins were not assayed.

Tissue Preparation and Neurochemical-Metabolite Analysis. Animals were sacrificed (CO_2), brains were collected immediately (over ice), weighed (brain weight), and analyzed for neurochemicals and metabolites (13, 14). The compounds quantitated using high-performance liquid chromatography with electrochemical detection were norepinephrine (NEpi), dihydroxyphenylalanine (DOPA), dihydroxyphenylacetic acid (DOPAC), dopamine (DA), 3-methoxytyramine (3-MT), 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and serotonin (5-HT). Standards were obtained from Sigma (St. Louis, MO) and the results are reported as the free compounds (ng compound/g brain tissue). Complete necropsy was performed on all animals and only results for Experiment 3 are reported here. Histopathology and selected serum chemistry (alanine aminotransaminase, aspartate aminotransaminase, alkaline phosphatase, bilirubin) for Experiments 1 and 2 have been reported (8, 15). The liver and kidneys were processed for microscopic examination. The brains of five randomly selected animals per group in Experiment 3 were processed for microscopic examination after staining with hematoxylin and eosin and luxol fast blue.

Statistical Analysis of the Data. Neurotransmitters and metabolite concentrations, brain weight (BRW), body weight (BOW), and BRW/BOW ratios were analyzed by analysis of variance (SAS Institute, Inc., 1982). Duncan's multiple range test was used to locate mean differences ($P < 0.05$). Food consumption was analyzed by appropriate methods as reported previously (8).

Results

Experiment 1. The CS-1 animals had decreased BOW ($P < 0.01$), increased BRW/BOW ($P < 0.01$) ratios, and increased 5-HIAA ($P < 0.01$) and 5-HIAA/5-HT ($P < 0.05$) ratios (Table I). Also, CS-1 rats had increased DOPA ($P < 0.01$), DOPAC ($P < 0.05$), and HVA ($P < 0.01$) whereas only DOPA and HVA were increased ($P < 0.01$) in the CS-2 rats.

Experiment 2. The 16% FM rats had decreased BOW ($P < 0.01$) and increased BRW/BOW ($P < 0.01$) ratios (Table II). These differences were associated with increased ($P < 0.01$) 5-HIAA, 5-HT, and 5-HIAA/5-HT ratios. Also, 3-MT was increased ($P < 0.05$) by treatment.

Experiment 3. Rats maintained on the 20% FM diets had decreased BOW ($P < 0.01$, Fig. 1), increased BRW/BOW ($P < 0.01$) ratios, and increased 5-HIAA ($P < 0.01$) and 5-HIAA/5-HT ($P < 0.05$) ratios compared with those consuming 20% corn (Table III). Similar differences were observed when the 20% FM animals were compared with groups fed the 5% FM

Table I. Neurotransmitters and Metabolites of Rats Fed Corn Infected with *Fusarium moniliforme*

Compounds[a]	Commercial corn[b]	CS-1[c]	CS-2[d]
NEpi	577 (81)	634 (68)	599 (94)
DOPA	34 (9)	55 (8)[e]	52 (12)[e]
DA	707 (77)	809 (81)	736 (51)
DOPAC	111 (21)	149 (31)[f]	117 (16)
HVA	67 (10)	97 (11)[e]	92 (9)[e]
3-MT	66 (6)	68 (8)	67 (8)
5-HIAA	411 (39)	585 (128)[e]	483 (45)
5-HT	346 (25)	396 (40)	356 (40)
5-HIAA/5-HT	1.19 (0.12)	1.47 (0.23)[f]	1.33 (0.14)
BRW (mg)	1680 (116)	1585 (88)	1690 (28)
BOW (g)	177 (11)	147 (8)[e]	184 (8)
BRW/BOW	9.48 (0.36)	10.82 (1)[e]	9.19 (0.26)

[a] ng/g brain (±SD).
[b] Seed corn (Adams Brisco Seed Co., Jackson, GA).
[c] Corn screenings associated with ELEM via Dr. S. Kasten, Illinois Department of Agriculture.
[d] Corn screenings associated with ELEM via Dr. F. Galey, University of Illinois, Urbana, IL.
[e] Different from controls: $P < 0.01$ ($n = 5$/group).
[f] Different from controls: $P < 0.05$ ($n = 5$/group).

Table II. Neurotransmitters and Metabolites of Rats Fed 16% *Fusarium moniliforme* (MRC 826) Cultured on Corn

Compounds[a]	Rat chow[b]	Experimental[c]
NEpi	614 (56)	619 (97)
DOPA	46 (12)	54 (27)
DA	749 (82)	817 (116)
DOPAC	144 (35)	146 (47)
HVA	77 (13)	81 (24)
3-MT	50 (8)	60 (11)[d]
5-HIAA	354 (35)	568 (93)[e]
5-HT	326 (13)	363 (49)[e]
5-HIAA/5-HT	1.09 (0.11)	1.58 (0.25)[e]
BRW (mg)	1758 (82)	1715 (96)
BOW (g)	312 (29)	218 (15)[e]
BRW/BOW	5.66 (0.44)	7.90 (0.38)[e]

[a] ng/g (±SD) of brain.
[b] Certified rat chow (Agway Inc., Waverly, NY), $n = 12$ animals.
[c] FM (MRC 826) cultured on corn (Athens Seed Co., Athens, GA) and added to rat chow at 16% (w/w) of the diet ($n = 8$ animals).
[d] Different from controls: $P < 0.05$.
[e] Different from control: $P < 0.01$.

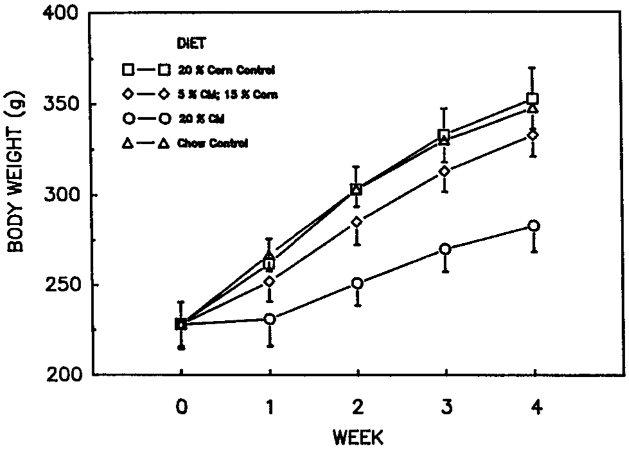

Figure 1. Body Weight (g ± SD) with time (weeks) of rats fed FM culture on corn (CM) and added to certified rodent chow. Twenty percent corn control = 20% corn/80% rodent chow; 5% CM-15% corn = 5% FM CM/15% corn/80% rodent chow; 20% CM = 20% FM CM/80% rodent chow.

Table III. Neurotransmitters and Metabolites of Rats Fed 5% and 20% *Fusarium moniliforme* (MRC 826) Cultured on Corn Compared with a 20% Corn/Rat Chow and Rat Chow Diets

Compounds[a]	Rat chow[b]	20% Corn[c]	5% FM[d]	20% FM[e]
NEpi	680 (30)	646 (95)	675 (64)	698 (73)
DOPA	33 (9)	41 (14)	41 (11)	34 (7)
DA	893 (46)	859 (113)	910 (38)	943 (101)
DOPAC	122 (29)	102 (30)	118 (36)	131 (46)
HVA	82 (11)	75 (11)	83 (14)	91 (17)
3-MT	45 (8)	43 (6)	45 (6)	50 (5)
5-HIAA	420 (36)	409 (48)	434 (53)	482 (46)[f]
5-HT	419 (34)	401 (64)	411 (21)	425 (37)
5-HIAA/5-HT	1.00 (0.04)	1.04 (0.13)	1.06 (0.11)	1.14 (0.00)[g]
BRW (mg)	1776 (56)	1808 (94)	1788 (101)	1720 (91)
Bow (g)	357 (12)	352 (18)	345 (17)	290 (22)[f]
BRW/BOW	4.98 (0.20)	5.14 (0.33)	5.19 (0.28)	5.96 (0.56)[f]

[a] ng/g brain (±SD).
[b] Certified rat chow (Agway Inc., Waverly, NY).
[c] Twenty percent corn (Adams Brisco Seed Co., Jackson, GA) added (w/w) to rat chow.
[d] Five percent FM (MRC 826) + 15% corn added (w/w) to rat chow.
[e] Twenty percent FM (MRC 826) added (w/w) to rat chow.
[f] Different from controls: $P < 0.01$ ($n = 10$ animals/group).
[g] Different from controls: $P < 0.05$ ($n = 10$ animals/group).

and the rodent chow diets. No differences were observed among the 5% FM, 20% corn, and rat chow diets (i.e., BRW, BOW, neurotransmitter and metabolite concentrations and ratios). Food consumption was reduced in the 5% and 20% FM animals (Fig. 2). Liver lesions including focal hepatocellular necrosis, hepatocellular hypertrophy, pyknotic and karyorrhectic nuclei, anisonucleosis, sporadic mitotic figures, and bile duct proliferation were present in all animals on the 20% FM diet and in 2 of 15 animals on the 5% FM diet. Cortical tubular nephrosis was present in 13 and 15 rats ($n = 15$) fed the 5% and 20% FM diets, respectively. No microsocpic lesions were found in brains.

Discussion

Elevated concentrations of 5-HIAA with elevated 5-HIAA/5-HT ratios produced by feeding FM-containing diets are consistent with impaired 5-HT metabolism and/or 5-HIAA elimination. Impaired cellular metabolism in the central nervous system involves alterations in concentration and turnover rates of the catecholamines and indoleamines (17). Elevation of 5-HT and 5-HIAA with increased 5-HIAA/5-HT ratios has been associated with neuropathy (methylmercury poi-

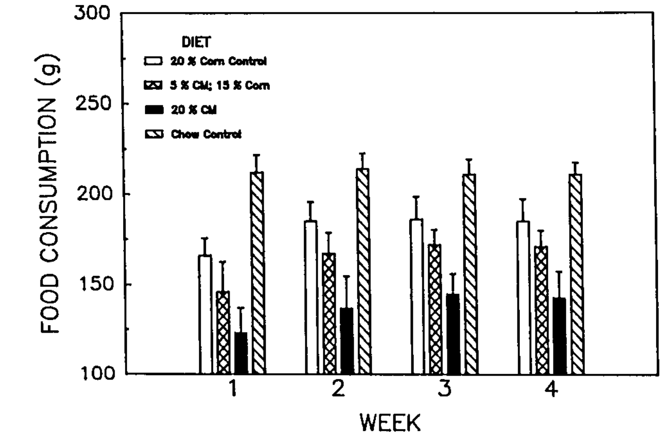

Figure 2. Food consumption (g ± SD) with time (weeks) of rats fed FM culture on corn (CM) and added to certified rodent chow. Twenty percent corn control = 20% corn/80% rodent chow; 5% CM-15% corn = 5% FM CM/15% corn/80% rodent chow; 20% CM = 20% FM CM/80% rodent chow.

soning) in rats and in premature rats fed protein-deficient diets (17, 18). Mercury and lead were not detected in the corn diets and the concentration of corn and FM culture material in the diets did not exceed 20%. Voss found (unpublished results) a corn rodent chow diet (1:1, w/w) had no effect on growth, maturation, liver histology, or serum chemistry (aspartate aminotransaminase, alanine aminotransaminase, alkaline phosphatase, and bilirubin) of 4- to 5-week-old rats when fed for an additional 4 weeks. In the current study, body weight was not decreased by the 20% corn/chow versus rodent chow diets (Fig. 1) and there were no differences in 5-HT, 5-HIAA, or the 5-HT/5-HIAA ratios between the rats on the CS-2 and corn diets (Table I). Then too, there were no apparent differences in the neurotransmitters or metabolites among the animals on the 20% corn/chow, 5% FM-15% corn/chow, and rodent chow diets (Tables II and III). Food consumption was consistently decreased in those groups fed 5% or 20% FM diets (fig. 2) and transiently decreased (Week 1 only) in those groups fed CS-1 and CS-2 diets (8); however, BRW among experimental groups (Tables I–III) and their controls were similar. The increases in BRW/BOW in the absence of BRW changes reflect brain tissue conservation during BOW loss. Edema, loss of myelin, and/or atrophy were not found during histopathologic examination of the brain. Neurotransmitter and metabolite concentrations would be affected by all of the above.

Diet-related increases in brain 5-HIAA could occur if low precursor availability (i.e., 5-HT) existed in the brain. Increased 5-HT metabolism could also result in decreased levels of 5-HT (19). These situations are unlikely since the brain concentrations of 5-HT in the experimental animals (Tables I and III) are not significantly different and the brain concentrations of 5-HT in the rats fed the 16% FM diet are increased ($P < 0.01$, Table II) as compared with their controls. The incidences of microscopic liver lesions typically seen after feeding FM culture material (3, 8) are similar in those rats fed FM-contaminated corn or cultured diets. Since the liver plays an essential role in the metabolism of 5-HT and its precursor tryptophan, the increase in brain 5-HIAA and the 5-HIAA/5-HT ratios may be secondary to altered hepatic tryptophan metabolism. Prior investigation (19) has shown subtle increases in brain 5-HT with significant increases in 5-HIAA (as observed in the current investigations) coincide with elevated concentrations of peripheral tryptophan. Subtle increases in brain 5-HT with significant increases in 5-HIAA is a response to lipolysis (18); therefore, the rats may be shunting more tryptophan to the brain at the expense of the periphery. This could explain the differences in BOW among the FM-treated animals and their respective controls (Table I–III).

The increases in DOPA and HVA in Experiment 1 (CS-1 and CS-2 animals) were not observed in Experiments 2 and 3. Increases in 3-MT in Experiment 2 were not observed in Experiments 1 or 3 (Tables I–III). These inconsistent differences in the DA precursor (DOPA) and DA metabolites (DOPAC, 3-MT, HVA) throughout the studies may be the results of biologic or experimental variations among the animals. Differences in naturally contaminated corn (CS-1, CS-2) and the fungal strain cultured in the laboratory also may be a consideration in the production of other toxins. What effect the individual fumonisins in the FM-contaminated corn and MRC 826 culture material have on neurotransmitters and metabolites is unknown. The different concentrations of fumonisins B_1 and B_2 (R. D. Plattner, personal communication; 12) in the diets and the different infection patterns of FM within the corn kernels of CS-1 (external and internal) and CS-2 (internal) could explain the quantitative differences observed in toxicity among the experiments. Fumonisin B_1 in CS-1 (Experiment 1) and in 20% FM (Experiment 3) diets was essentially equivalent. The CS-2 diet (Experiment 1) contained 14 μg/g fumonisin B_1 and the 5% FM (Experiment 3) contained approximately 35 and 33 μg/g (extrapolated values) of fumonisins B_1 and B_2, respectively. The 16% FM diet may have contained a higher concentration of these compounds predicated on the differences in both culture substrate (i.e., different varieties of corn) and culture conditions. These varying concentrations of fumonisins among the experimental treatments would suggest a dose-related response. Therefore, the elevated 5-HIAA concentrations and 5-HIAA/5-HT ratios appear to be Fusarium and not diet related. Moreover, the different nature of the strains and their production of other secondary metabolites may potentiate the final overall effect observed in this study. Zearalenone possesses estrogenic and anabolic activity (20); however, the concentrations in CS-2 are more than two times those of CS-1 and was dismissed as contributing to the observed effects.

Monitoring brain 5-HT, 5-HIAA, and 5-HIAA/5-HT ratios in rats may be a useful bioassay for the FM toxins and warrants further investigations.

The authors thank L. K. Tate, N. B. Brice, R. M. Bennett, P. M. Hayes, and P. C. Stancel for technical assistance during the course of these studies.

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