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Alloxan-Induced Glucoprivic Feeding Deficits are Blocked by D-Glucose and Amygdalin

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MURNANE, J. M. AND S. RITTER. *Alloxan-induced glucoprivic feeding deficits are blocked by D-glucose and amygdalin.* PHARMACOL BIOCHEM BEHAV **22**(3) 407–413, 1985.—Intracerebroventricular injection of alloxan, a pancreatic beta (B) cell cytotoxin, impairs glucoprivic feeding in rats. The goal of this experiment was to determine whether alloxan-induced impairment of glucoprivic feeding can be attenuated by agents which antagonize alloxan's toxicity in the B cell. Therefore, alloxan was co-administered into the fourth ventricle alone or in combination with D-glucose, L-glutamine, or amygdalin, all known antagonists of alloxan's B cell toxicity, or with L-glucose, which does not antagonize B cell toxicity. We found that alloxan produced deficits in glucoprivic feeding which were not attenuated by co-administration with L-glucose or L-glutamine. Alloxan/L-glucose treated rats ate 11% and 14% of control intake, respectively, after systemic administration of 2-deoxy-D-glucose (2DG, 250 mg/kg) and fourth ventricular 5-thioglucose (5TG, 120 μg/5 μl). Alloxan/L-glutamine rats ate 20% and 22% of control intake after 2DG and 5TG, respectively. In contrast, D-glucose and amygdalin (15 mM) completely blocked alloxan-induced impairment of glucoprivic feeding and amygdalin (10 mM) exerted a partial protective effect. These behavioral results may indicate that in the brain, susceptibility to alloxan toxicity depends upon cellular characteristics shared with the B cell.

Glucoprivic feeding Alloxan 2-Deoxy-D-glucose 5-Thioglucose Beta cell Rats

THE glucoprivic control of food intake was first postulated by Smith and Epstein who observed that a sudden decrease in glucose utilization (glucoprivation) brought about by injection of the glucose antimetabolite, 2-deoxy-D-glucose (2DG), was associated with a dramatic increase in food intake in rats and monkeys [13,51]. Subsequent experiments have demonstrated the glucoprivic control of feeding in many mammalian species, including humans [28–30, 51, 53]. The fact that intracerebral administration of glucoprivic agents stimulates feeding at doses which are ineffective systemically clearly indicates that this control is mediated by glucoreceptor cells that reside in the brain [4, 12, 34]. Although impairment of glucoprivic feeding results from chemical, mechanical, or electrolytic damage in a rather large number of forebrain structures [1, 2, 6, 8, 14, 21, 33, 52, 56], it now appears that the glucoreceptors themselves are localized in the caudal hindbrain [18,41].

Recently, it has been demonstrated that intraventricular administration of the pancreatic beta (B) cell cytotoxin, alloxan [11,22], produces long-lasting deficits in glucoprivic feeding without producing other apparent behavioral or ingestive impairment [42,60]. We have speculated that alloxan-induced deficits may arise from selective damage to neurons involved in glucoprivic feeding, rather than from generalized neurotoxic damage. This speculation is based in part on our observation that glucoprivation-induced hyperglycemia and angiotensin-induced drinking, both mediated by periventricular receptors, are not impaired by alloxan [42]. Furthermore, the fact that subtoxic intraventricular doses of alloxan stimulate feeding suggests that alloxan interacts with the glucoreceptor cells which control glucoprivic feeding, rather than with some other component of the neural machinery involved in the feeding response [43]. Although the brain cells which are damaged by alloxan have not yet been identified, the possibility that alloxan may exert a selective cytotoxic action against brain glucoreceptors controlling glucoprivic feeding is consistent with alloxan's action in other tissues. Under appropriate conditions of administration and dose, alloxan produces a relatively selective cytotoxic destruction of glucose-sensitive pancreatic B cells after systemic administration [11,31] and, when applied locally to the tongue, produces a selective blockade of lingual glucoreception [61].

Because of alloxan's potential usefulness as a tool for studying glucoprivic feeding, it is important to identify its mode of action in the brain. However, the mechanism of alloxan's cytotoxic action in brain cannot be directly investigated since alloxan's target cells in the brain have not yet been anatomically localized. Therefore, we have attempted in the present experiment to further characterize alloxan's

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mode of action in the brain by co-administering it into the ventricle with a number of substances known to antagonize its cytotoxic action in the pancreatic B cell. Through these experiments we hoped to determine indirectly whether alloxan exerts its cytotoxic effects on pancreatic and brain target cells by similar mechanisms. We determined previously that intraventricular co-administration of alloxan with D-glucose, a substance which antagonizes alloxan's diabetogenic effect [47,62], completely blocked alloxan-induced impairment of glucoprivic feeding [46]. In this experiment we examined two additional B cell protective agents with diverse chemical characteristics, L-glutamine [48] and amygdalin [26], α-([6-β-O-D-glycopyranosyl-β-D-glucopyranosyl]oxy) benzenoacetonitrile, and one nonprotective agent, L-glucose [44], for their ability to protect the glucoprivic feeding response from alloxan-induced impairment.

METHOD

Adult male Sprague-Dawley rats weighing approximately 400 g were used. All animals were housed individually in suspended wire mesh cages and maintained on a 12 hour light-dark cycle (lights on from 0600–1800) in a temperature-controlled room (21±0.05°C). Pelleted rat food and water were available ad lib, except during experiments. Tests were conducted in the animals home cages beginning at 0900 hours. The fourth ventricle was used in this experiment as the site for injection of all test substances because of convincing evidence localizing glucoreceptors controlling glucoprivic feeding in the caudal hindbrain [18,41] and our previous observation that fourth ventricular alloxan injections produced greater deficits in glucoprivic feeding than lateral ventricle injections [42]. Therefore, prior to experimentation the animals were anesthetized and stainless steel guide cannulas containing removable obturators were stereotaxically placed in the fourth ventricle. Coordinates used were 0.0 mm lateral to midline, 2.0 mm rostral to the occipital crest and 7.5 ventral to the brain surface. During intracerebroventricular injections the obturators were replaced by a 30 gauge injector that extended 0.75 mm beyond the tip of the guide cannula. Solutions were delivered via a microliter syringe connected to the injector tip by polyvinyl tubing. After recovery from surgery animals were tested for 5-thio-D-glucose (5TG) induced feeding in a 2 hour test. 5TG is an antiglycolytic agent which has been shown to induce feeding and increase blood glucose concentration when injected into the fourth ventricle [50]. The presence of a feeding response after injection of a low dose of 5TG through an implanted cannula indicates cannula patency and proximity to glucoreceptor cells. Only rats which ate at least 1.0 gram of food more after 5TG than after saline were included in this study.

Preliminary studies were then conducted to identify possible toxic effects of intraventricular L-glucose, amygdalin, and L-glutamine, or direct effects of these substances on feeding or blood glucose. For these studies, L-glucose (3 M), amygdalin (10 and 15 mM) and L-glutamine (10 and 15 mM) were administered as they would be when co-injected with alloxan except that alloxan was not administered. Feeding and blood glucose were measured hourly for three hours following the injections, as described below. During the ensuing week, the rats were tested for 2DG-induced feeding (as described below) to assure that these test substances had not impaired the ability of animals to respond to a glucoprivic stimulus.

When preliminary testing was complete, the experimental animals were assigned to one of the eight treatment groups. On group of rats (n=11) was injected with alloxan alone. Alloxan (Sigma, 200 μg) was dissolved in ice-cold, acidified saline (pH 3.0) to prevent degradation [37] and injected immediately into the fourth ventricle. In two additional groups, alloxan was co-injected with D- or L-glucose (n=5 and 6, respectively). For these treatments, alloxan (200 μg) was dissolved in a 3 M glucose solution (pH 3.0). Two groups were injected with alloxan (200 μg) dissolved either in a 10 or 15 mM L-glutamine solution (pH 3.0, n=6 and 5, respectively). Two more groups were co-injected with alloxan plus amygdalin (Sigma, 10 and 15 mM, n=6 and 5, respectively). Amygdalin was prepared in saline (pH 7.0) and injected 5 min prior to alloxan, since amygdalin readily hydrolyzes at acidic pH's. Controls (n=12) received an injection of saline (0.9%, pH 3.0).The injection volume was 5 μl in all cases. The concentrations of alloxan and the potential protective agents were established by extrapolation from studies of B cell toxicity [24, 51, 53, 61] and our own previous work. A higher dose of alloxan was used in this work than previously [42,60] to provide a more stringent test of the protective agents.

After recovery of pre-injection body weights, feeding and blood glucose responses were measured in all rats after subcutaneous injection of 2-deoxy-D-glucose (2DG, Sigma, 200 mg/kg) or fourth ventricular injection of 5TG (120 μg in 5 μl saline). Since all 47 animals could not be tested at the same time, the control group was divided. One group of controls was tested with the alloxan/amygdalin and alloxan/L-glutamine treated animals and the remaining controls were tested with the other treatment groups. Feeding was measured hourly beginning one hour prior to and ending three hours after administration of drugs or saline by weighing remaining pellets and spilled crumbs to the nearest 0.1 g. Blood glucose was measured in separate tests after administration of 2DG, 5TG, and saline. Blood samples (50 μl) for glucose analysis were collected from the tail vein 0, 60, 120, and 180 minutes following 2DG, 5TG, and saline administration and analyzed using the glucose oxidase method [45]. Feeding and blood glucose tests with 2DG and 5TG were conducted in a random order.

After all tests were completed, rats were anesthetized and red ink (5 μl) was injected into the fourth ventricle through their cannulas. Subsequently, the rats were deeply anesthetized, exsanguinated, and perfused with 10% buffered formalin. Finally, the brains were carefully removed, dissected, and the pattern of ink distribution was examined microscopically to verify cannula placement. For analysis of the feeding tests, the intake after saline (mean of two tests) was subtracted from the intake after 2DG or 5TG for each rat and the results were subjected to analysis of variance and Dunnett's multiple range test. Student's *t*-test was used to isolate significant differences in blood glucose responses.

RESULTS

Our preliminary studies showed that both the higher and lower doses of amydalin and L-glutamine stimulated some feeding when administered alone into the fourth ventricle (Table 1). Only amygdalin produced a rise in blood glucose. In one test, amygdalin produced a rise in blood glucose of 45 mg% above baseline levels ($p<0.01$) one hour after the injection (Table 1). However, Table 2 shows that no hyperglycemia was observed when the experiment was replicated. Table 2 also shows the blood glucose responses to 5TG, injected subsequently through the same cannulas, to

TABLE 1

EFFECTS OF FOURTH VENTRICULAR INJECTION (5 μl) OF POTENTIAL ALLOXAN ANTAGONISTS ON FOOD INTAKE (MEAN OF 2 TESTS) AND BLOOD GLUCOSE CONCENTRATION

	Blood Glucose (mg% ±S.E.M.) Time (min)				Food Intake (g) Time (min)
Treatment	0	60	120	180	0–180
Saline	90 ± 5	90 ± 8	89 ± 3	90 ± 3	0.4 ± 0.1
D-glucose (3 M)	88 ± 4	99 ± 4	93 ± 4	90 ± 3	
L-glucose (3 M)	91 ± 5	101 ± 5	86 ± 7	99 ± 5	0.1 ± 0.01
L-glutamine (10 mM)	86 ± 2	89 ± 2	89 ± 3	82 ± 6	2.0 ± 0.3*
L-glutamine (15 mM)	90 ± 3	91 ± 2	90 ± 2	86 ± 2	2.8 ± 0.3*
Amygdalin (10 mM)	90 ± 3	136 ± 4*	120 ± 4*	100 ± 2	2.0 ± 0.1*
Amygdalin (15 mM)	94 ± 1	131 ± 10*	116 ± 6*	101 ± 4	1.8 ± 0.1*

*$p<0.01$ vs. saline, bidirectional t-test.

TABLE 2

BLOOD GLUCOSE CONCENTRATIONS OF 10 RATS AFTER FOURTH VENTRICULAR INJECTIONS OF SALINE (5 μl), AMYGDALIN (15 mM, 5 μl, pH 7.0), AND 5-THIOGLUOCSE (5TG, 105 μg IN 5 μl)

	Blood Glucose (mg %) Time (min)				
Treatment	−15	10	30	45	60
Saline	70 ± 2	77 ± 3	71 ± 2	73 ± 2	76 ± 2
Amygdalin	73 ± 2	74 ± 2	73 ± 2	73 ± 2	74 ± 2
5TG	71 ± 2	93 ± 5	163 ± 16	180 ± 19	180 ± 19

indicate the cannula's patency and proper location. Rats appeared somewhat agitated after L-glutamine injections but did not become hyperglycemic. The food intake of animals injected with amygdalin and L-glutamine did not differ from controls when they were subsequently tested with 2DG. Saline-injected animals ate 3.4±0.2 g of food in the 2DG test. Animals previously injected with the test substances ate the following amounts of food in the 2DG test: 10 mM amygdalin, 3.3±0.1 g; 15 mM amygdalin, 3.1±0.2 g; 10 mM L-glutamine, 3.2±0.1 g; 15 mM L-glutamine, 3.1±0.2 g. These data indicate that the test substances themselves did not damage neural substrates involved in glucoprivic feeding.

As reported previously [42], some alloxan-treated rats showed a transient reduction in body weight which appeared to be secondary to a vestibular-like syndrome involving disequilibrium and abnormal postural reflexes. Body weights returned to normal in these animals within three weeks and were indistinguishable from controls when testing was initiated.

The two control groups did not differ in their feeding responses to 2DG and 5TG and their feeding data were therefore pooled for statistical analysis. Controls ate 4.5±0.4 and 3.6±0.3 g of food above their saline intake in response to 2DG and 5TG, respectively. As reported previously, alloxan significantly impaired the glucoprivic feeding response. Figure 1 shows that alloxan-treated rats ate only 0.6±0.2 g above their saline intake in response to 2DG and 1.1±0.3 g in response to 5TG. These responses were 13% and 31% of the amount eaten by controls in these tests. Co-administration of L-glucose with alloxan did not attenuate alloxan-induced deficits in glucoprivic feeding. Alloxan/L-glucose rats ate 11% and 14% of control intake, or 0.5±0.3 g and 0.4±0.4 g, in response to 2DG and 5TG, respectively. Similarly, neither dose of L-glutamine protected against alloxan-induce deficits. Since the two dosage groups showed similar effects of alloxan they were pooled for further statistical analysis. Alloxan/L-glutamine rats ate 20% and 22% of control intake, or 0.9±0.2 and 0.8±0.1 g after 2DG and 5TG, respectively. In contrast, both D-glucose and amygdalin protected against alloxan-induced deficits in glucoprivic feeding. The protective effect of amydalin was dose-related. As Fig. 1 indicates, food intake in alloxan/D-glucose and alloxan/amygdalin (15 mM) animals did not differ significantly from control intakes after 2DG or 5TG. The lower dose of amygdalin (10 mM) also attenuated the effects of alloxan, but to a lesser extent.

As previously reported [42,43], we found that alloxan did not impair either the magnitude or the temporal aspects of the hyperglycemic response to glucoprivation. Table 3 shows the hyperglycemic responses to 2DG and 5TG of the animals treated with alloxan and alloxan/D-glucose and their saline controls. Table 4 shows the blood glucose values of

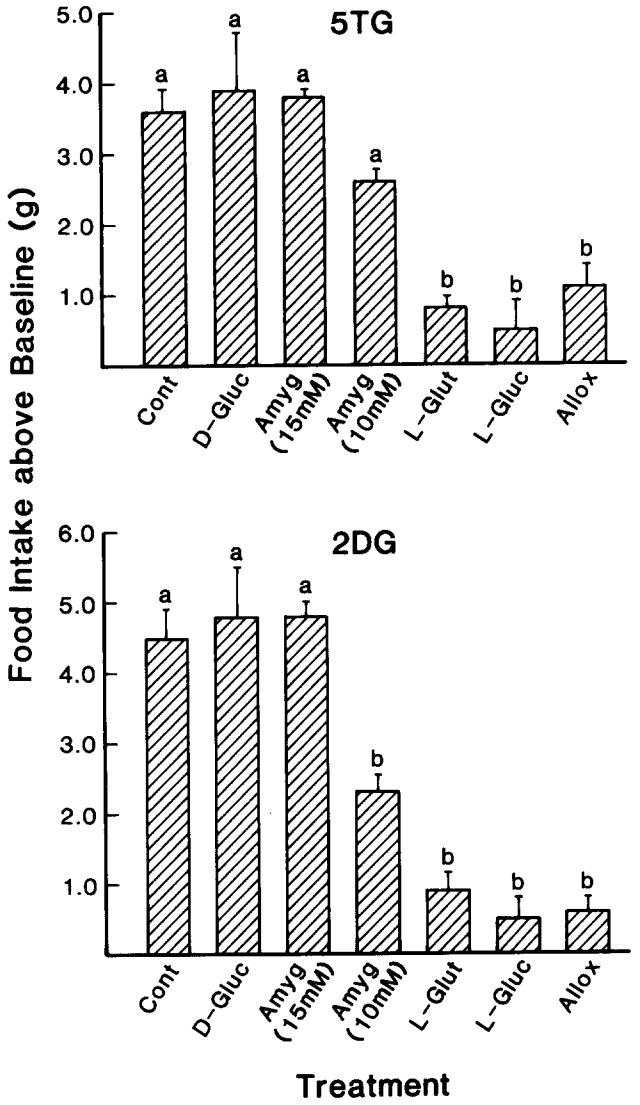

FIG. 1. Food intake after systemic administration of 2-deoxy-D-glucose (2DG, 250 mg/kg, SC) and fourth ventricular administration of 5-thioglucose (5TG, 120 μg in 5 μl) in rats previously given fourth ventricular injections of alloxan (Allox), saline vehicle solution (Cont), or alloxan in combination with one of the following substances: D-glucose (D-Gluc), L-glucose (L-Gluc), 15 mM amygdalin (Amyg 15 mM), 10 mM amygdalin (Amyg 10 mM), or L-glutamine (L-Glut). Intakes after saline injections (less than 1 gram in all cases) have been subtracted from the intakes after 2DG and 5TG. Within each panel, the feeding responses of the treatment groups designated by a common letter above the bar do not differ significantly from one another, but those with different letters differ at $p<0.05$ using Dunnett's procedure. The pooled variances for the 2DG and 5TG tests are 0.9096 and 0.8935, respectively.

animals treated with alloxan/L-glutamine and alloxan/amygdalin and their saline-injected controls. Responses of the treated animals did not differ from their corresponding saline-treated controls at any time point.

Analysis of histological results assured that the cannula tracks of all rats included in this study terminated in the fourth ventricle. Distributions of the red dye injected through the cannulas prior to death confirmed the accurate location and patency of all cannulas.

DISCUSSION

Our results show that fourth ventricular injection of amygdalin protects against alloxan-induced deficits in glucoprivic feeding. Glucose also protects against alloxan and this effect is stereospecific for the D-isomer. Since amygdalin and D-glucose antagonize alloxan's diabetogenic effects [16, 26, 38, 44], our results may indicate that alloxan impairs glucoprivic feeding by a cytotoxic mechanism similar to that exerted by alloxan in the B cell. Although alloxan's cytotoxic mechanisms in the brain and pancreas may be similar, they nevertheless do not appear to be identical since L-glutamine, a known antagonist of alloxan in the B cell [48], does not attenuate alloxan-induced impairment of glucoprivic feeding.

Biochemical explanations for alloxan's selective toxicity for the B cell are still speculative and controversial [16]. However, strong evidence indicates that B cell susceptibility to alloxan is largely attributable to the concurrence of two cellular characteristics [32]: (1) the ability of the B cell to rapidly accumulate high concentrations of alloxan [19,59]; and (2) the B cell's relative inability to reduce the highly cytotoxic radicals which are formed by the intracellular metabolism of alloxan [7,25]. Accordingly, antagonism of alloxan's toxicity in the B cell appears to be related to the ability of alloxan antagonists to decrease the intracellular accumulation of alloxan or its toxic metabolites. Thus, D-glucose and other metabolizable substances are thought to antagonize alloxan-induce toxicity in the pancreas by stimulating intracellular metabolism and increasing the generation of reducing equivalents. such as NADPH [9, 15, 16, 48]. These reducing equivalents might then protect the cell by reducing the toxic free radicals generated by alloxan metabolism. Similarly, the ability of amygdalin to protect against alloxan's B cell toxicity may be related to its ability to act as a free radical scavenger [26]. The fact that several other free radical scavengers have been shown to antagonize alloxan's diabetogenic effect would support this view [16, 17, 20, 25].

By analogy with the B cell, we might speculate that D-glucose and amygdalin protect against alloxan-induced deficits in glucoprivic feeding by the same mechanisms described above: D-glucose through its stimulation of intracellular metabolism and amygdalin through its direct action as a free radical scavenger. However, intraventricular injection of amygdalin was followed by mild hyperglycemia in some cases, as has been observed after systemic amygdalin administration [26]. Therefore, we must also consider the possibility that in our experiment amygdalin acted indirectly to protect the glucoprivic feeding response by elevating blood glucose. Though this possibility would be consistent with the fact that D-glucose protects against alloxan toxicity in the brain, it nevertheless seems unlikely that this route of action could account for our results with amygdalin. First, in our hands, the hyperglycemic response to amygdalin was a spurious one, not consistently obtained. Second, to be effective against alloxan's diabetogenic effect, glucose must be elevated prior to or simultaneously with alloxan administration. The protective effect of glucose is totally lost if it is administered as little as five minutes after alloxan injection [39,55]. Third, the degree of hyperglycemia we observed was probably inadequate to exert a protective action [59]. Therefore, although it is possible that amygdalin may have caused

TABLE 3

HYPERGLYCEMIC RESPONSES TO SYSTEMIC 2-DEOXY-D-GLUCOSE (2DG, 250 mg/kg, SC) AND FOURTH VENTRICULAR 5-THIOGLUCOSE (5TG, 120 μg/5 μl) IN RATS AFTER FOURTH VENTRICULAR TREATMENT WITH SALINE, ALLOXAN (200 μg IN 5 μl), OR ALLOXAN IN COMBINATION WITH 3 M D-GLUCOSE (5 μl)

	Blood Glucose (mg % ±S.E.M.)							
	2DG				5TG			
	Time (min)				Time (min)			
Treatment	0	60	120	180	0	60	120	180
Saline	95 ± 21	271 ± 9	254 ± 9	191 ± 9	98 ± 2	194 ± 20	166 ± 11	161 ± 17
Alloxan	97 ± 8	276 ± 20	236 ± 10	212 ± 7	98 ± 2	223 ± 18	191 ± 5	150 ± 16
Alloxan/ D-glucose	96 ± 2	292 ± 13	242 ± 15	181 ± 5	96 ± 2	206 ± 13	180 ± 10	150 ± 3

TABLE 4

HYPERGLYCEMIC RESPONSES TO SYSTEMIC 2DG (250 mg/kg SC) AND FOURTH VENTRICULAR 5TG (120 μg IN 5 μl) IN RATS AFTER FOURTH VENTRICULAR TREATMENT WITH SALINE OR WITH ALLOXAN (ALLOX) IN COMBINATION WITH L-GLUTAMINE (GLUT) (10 OR 15 mM) OR AMYGDALIN (AMYG) (10 OR 15 mM)

	Blood Glucose (mg % ±S.E.M.)							
	2DG				5TG			
	Time (min)				Time (min)			
Treatment	0	60	120	180	0	60	120	180
Saline	85 ± 1	203 ± 7	168 ± 7	125 ± 5	86 ± 2	181 ± 8	142 ± 5	106 ± 3
Allox/glut (10 mM)	83 ± 2	202 ± 14	153 ± 5	106 ± 5	87 ± 2	192 ± 6	147 ± 6	106 ± 5
Allox/glut (15 mM)	80 ± 2	202 ± 12	158 ± 6	111 ± 7	86 ± 3	186 ± 7	137 ± 4	103 ± 5
Allox/amyg (10 mM)	78 ± 2	204 ± 10	171 ± 7	113 ± 5	90 ± 2	178 ± 11	148 ± 5	116 ± 5
Allox/amyg (15 mM)	80 ± 2	206 ± 13	160 ± 9	115 ± 7	85 ± 2	169 ± 7	139 ± 2	110 ± 4

a slight blood glucose rise during the hour following its co-administration with alloxan in our study, this elevation probably was not large enough or rapid enough to have been a significant factor in abolishing alloxan toxicity.

Since L-glutamine blocks the diabetogenic effect of alloxan [48], we expected that this substance would also protect against alloxan-induced impairment of glucoprivic feeding. But glutamine was not effective in preventing alloxan-induced impairment of glucoprivic feeding even though the concentrations of L-glutamine used in our study were high enough to produce transient signs of toxicity. However, even in the B cell, glutamine is a relatively weak protective agent [48] and it is possible that our concentration was not high enough to antagonize alloxan's effect in brain. Differences in the cellular uptake, compartmentalization or metabolic fate of glutamine [3] in brain and B cells might also account for the differences in its ability to protect these cells against alloxan-induced toxicity. Alternatively, our result may indicate that the mechanism of alloxan's toxicity in brain differs somewhat from its mechanism in the β-cell.

The suggestion that intraventricular injection of alloxan may selectively damage glucoreceptor cells controlling glucoprivic feeding, though indeed speculative, is consistent not only with our behavioral evidence [42,43], but also with alloxan's relative selectivity as a B cell cytotoxin after systemic administration [19,31]. However, alloxan's peripheral toxicity is not limited exclusively to the B cell and the fact that high systemic doses may also damage cells in the liver and kidney [11, 24, 36] underscores the necessity for further study of alloxan's effects in the brain. We are currently conducting additional anatomical studies which we hope will allow us to characterize further the neurotoxicity of alloxan after intraventricular administration. It is encouraging that the preliminary results of these studies have revealed no evidence of extensive damage of brain tissue by alloxan, despite its potential cytotoxicity for a variety of cell types.

The stimulation of feeding by fourth ventricular glutamine and amygdalin injection, observed in our pilot work, is interesting, and to our knowledge, has not been previously reported. Glutamine is a precursor for glutamate in both metabolic and neurotransmitter pools [5, 54, 57], but may be a precursor for other amino acid neurotransmitters as well. In addition, the physiological significance of the high glutamine doses we used might well be questioned. Nevertheless, it is tempting to speculate that elevation of brain glutamine levels may stimulate feeding by increasing the concentration of glutamate in glutaminergic nerve terminals involved in food intake. It might also be important to know

the mechanism by which amygdalin stimulates food intake. However, our experiments were not designed to examine these questions.

It is noteworthy that alloxan did not impair the blood glucose response typically observed during 2DG- and 5TG-induced glucoprivation. The rise in blood glucose during a glucoprivic challenge results from a centrally mediated stimulation of sympathoadrenal discharge and consequent stimulation of hepatic glycogenolysis by epinephrine. Previous work has indicated that receptors which trigger this response are located in the caudal hindbrain [10,41] and can be simulated by fourth ventricular administration of low 5TG doses [41,50]. The failure of alloxan to damage the blood glucose response in this study is consistent with previous evidence suggesting that the receptors for this response are not susceptible to alloxan at doses which abolish or greatly impair the glucoprivic feeding response, even though their response to fourth ventricular 5TG indicates that they lie within the diffusion path of a fourth ventricular infusate. Thus, it appears that not all populations of glucose-sensitive brain cells are susceptible to alloxan's cyctotoxicity, regardless of their anatomical proximity to the alloxan injection site.

In summary, these results suggest that in brain cells which are susceptible to alloxan toxicity, susceptibility is related to cellular characteristics shared with the B cell. Studies on the B cell may therefore provide a model for further, more definitive investigations regarding alloxan's precise mode of action in the brain. Such studies may provide clues regarding the operation of brain metabolic receptors controlling the glucoprivic feeding response.

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