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Further Analysis of the Resistance of the Diabetic Rat to d-Amphetamine

JOHN F. MARSHALL

Department of Psychobiology, University of California, Irvine
Irvine, CA 92717

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MARSHALL, J. F. *Further analysis of the resistance of the diabetic rat to d-amphetamine.* PHARMAC. BIOCHEM. BEHAV. 8(3) 281–286, 1978. – Rats that were made diabetic by the subcutaneous injection of alloxan monohydrate were found to be resistant to the anorexic action of d-amphetamine. This resistance to amphetamine anorexia did not appear attributable to an increased hunger motivation of the diabetic rats, but rather seemed due to a diminished action of the drug in alloxan-injected animals. This conclusion was supported by further experiments indicating that alloxan-injected rats show diminished locomotor activity and stereotyped behavior following amphetamine administration. Furthermore, the amphetamine resistance appears to be the result of the diabetic state, since amphetamine-induced stereotyped behavior could be reinstated in alloxan-injected rats by the administration of protamine zinc insulin for ten days. The results of these investigations suggest that there exists an altered central nervous system response to d-amphetamine in the diabetic rat. The possibility of an abnormal functioning of central catecholamine-containing neurons in such animals is discussed.

Alloxan Amphetamine Anorexic drugs Catecholamines Diabetes Feeding Insulin Locomotor activity Stereotyped behavior

THE most debilitating effects of clinical diabetes mellitus are the complications associated with the disease, in particular the nephropathy, retinopathy, and neuropathies. Although peripheral neuropathies involving both somatic and autonomic nerves have been frequently associated with the diabetic state [3], changes in the central nervous system have been noted only infrequently (e.g. [4,28]) and often appear secondary to cerebrovascular complications of the disease. Despite the fortunate rarity of obvious central neuropathology in diabetes, it may be that the metabolic disorder results in alterations of brain function which are structurally undetected. We [18] have recently reported that rats made diabetic by the injection of alloxan show marked alterations in their behavioral response to amphetamine, changes similar to those seen in animals with impaired functioning of brain dopamine-containing neurons. Specifically, diabetic rats showed less anorexia following a range of doses of d-amphetamine and showed less locomotor activity after 1 mg/kg of this compound than did controls. In addition, it was found that the anorexic effect of amphetamine could be restored by chronic administration of insulin to the alloxan-injected animals. Furthermore, the diminished response of the diabetic rat to amphetamine was not attributable to reduced levels of the drug in the plasma or brain.

In present experiments, I explore in greater detail the nature of the impaired behavioral responsiveness of diabetic rats to amphetamine. The results of these investigations suggest (1) that the resistance of the alloxan-injected rat to amphetamine's anorexic effect is not likely attributable to an increased hunger motivation associated with the diabetic state, (2) that diabetic rats show markedly less locomotor activity than do nondiabetics across a wide range of amphetamine doses, (3) that the diabetic animal is resistant to yet another behavioral action of amphetamine – its capacity to induced stereotyped behavior, and (4) that the stereotypy-inducing effects of amphetamine can be largely restored in alloxan-injected rats by chronic protamine zinc insulin administration.

EXPERIMENT 1: RESISTANCE OF ALLOXAN-DIABETIC RATS TO AMPHETAMINE-INDUCED ANOREXIA

Marshall, Friedman and Heffner [18] reported that alloxan-diabetic rats given amphetamine showed markedly less anorexia than did controls. In that experiment all rats were deprived of food overnight, and the effect of amphetamine on feeding was examined during the 45 min period after Purina chow was restored. One could argue, however, that the diabetic rat appears resistant to the anorexic action of amphetamine simply because it is hungrier than controls at the time of testing. This increased hunger could arise for two reasons. First, the normal rat economizes energy loss and mobilizes fat stores during overnight deprivation; however, the diabetic will lose more energy (due to glycosuria) and has meager fat stores to mobilize. Thus, when offered food following a fast, the diabetic animal might eat more than controls because of a greater need. In addition, it appears that many diabetics are more readily able to utilize fats than carbohydrates [12, 13, 25]. Therefore, a high-carbohydrate, low-fat diet such as Purina chow may be metabolically less useful to diabetics than to controls. It is possible that the diabetic rat might eat more of this diet following amphetamine than do

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controls because most of the calories are in a form which cannot be readily utilized.

In the present experiment I evaluated whether an increased hunger of the diabetic rats may contribute to their apparent resistance to amphetamine's anorexic action. The amount of feeding following amphetamine administration was measured in non-deprived diabetic and normal rats. In addition, the diet of the control animals was diluted with non-nutritive bulk (cellulose) so that both groups received a metabolically-diluted diet.

Method

Forty-one female rats (Zivic-Miller, Pittsburgh) weighing 230–280 g at the time of alloxan administration were used. Nineteen were etherized and given a subcutaneous injection of alloxan (200 mg/kg of the monohydrate). The remaining 22 were etherized but not injected. Starting 3 weeks later the diabetic rats were given Purina powder in jars. Controls were fed a diet of 4 parts by weight Purina powder mixed with 3 parts cellulose. After adaptation to these diets for 1–2 weeks, control animals ate approximately the same weight of diluted diet in 24 hours as diabetics ate of chow. At this time, testing began. Nondeprived rats of both groups were given isotonic saline or d-amphetamine (0.5 or 1.0 mg/kg of the salt) at the start of the dark part of a 12:12 cycle, and the amount of diet consumed in the next 90 minutes was measured. Injections of amphetamine were separated by at least 3 days.

At the conclusion of behavioral testing 3 of the diabetic and 7 control rats were killed by decapitation, and blood glucose analyses were performed (Worthington Glucostate Reagent Set).

Results and Discussion

Control animals showed a marked, dose-dependent decrease in food intake following amphetamine administration. In contrast, the diabetic rats show a substantial resistance to the anorexic effects of this compound (Fig. 1).

Blood glucose determinations yielded values of 119.1 ± 5.2 mg% for the 7 control rats, and 217, 572, and 601 mg% in the 3 diabetic animals sampled.

The resistance of the diabetic rat to amphetamine's anorexic action observed in this experiment corresponds closely to the resistance reported previously in food-deprived diabetics [18]. These findings argue strongly that the greater food intake seen in diabetic than in control rats given amphetamine cannot be attributed simply to a greater need of the diabetic rat for food. In the present work, both groups of animals had ad lib access to food 24 hours each day, so that food deprivation is ruled out as a complicating factor. Neither are the present findings consistent with the hypothesis that the greater feeding of the diabetic rat given amphetamine is due to their being fed a metabolically-diluted diet. Even though the control rats were adapted to and tested with a cellulose-diluted diet, they still showed a greater anorexia following amphetamine than did diabetics. The diabetic state appears to induce a true resistance to the behavioral effect of this compound, a conclusion which is supported by the subsequent experiments.

EXPERIMENT 2: RESISTANCE OF ALLOXAN-DIABETIC RATS TO AMPHETAMINE-INDUCED LOCOMOTOR ACTIVITY

In the present experiment I examine whether diabetic rats are resistant to the locomotor stimulant action of amphetamine, just as they are resistant to its anorexic action.

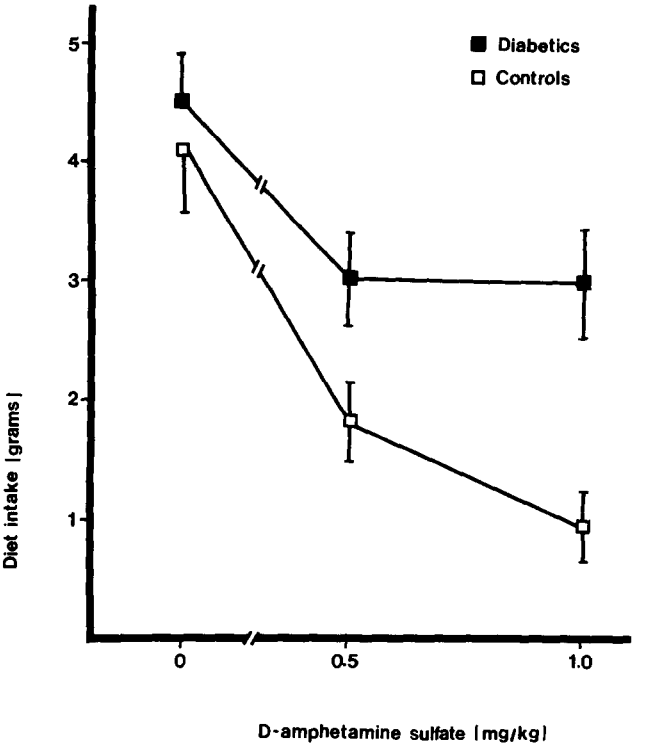

FIG. 1. Anorexia following d-amphetamine sulfate in non-deprived control or alloxan-diabetic rats. Controls were fed Purina powder-cellulose diet; diabetics were fed Purina powder. Ordinate depicts the amount of diet eaten during 90 min test. Mean ± SEM Student *t*-tests reveal that the control and diabetics differ significantly at the 0.5 ($p<0.02$) and 1.0 mg/kg ($p<0.001$) doses.

Method

Eleven female rats were used. Alloxan was administered as in the first experiment to 5; the other 6 received no injection. All were maintained on Purina pellets and water ad lib. Testing began two weeks later, at which time all the alloxan-injected rats but none of the controls had glycosuria in excess of 2% (Lilly Tes-Tapes). The rats were placed in activity wheels (Wahmann) for a 30 min adaptation period following which they were removed and given an intraperitoneal injection of isotonic saline or d-amphetamine (0.5, 1.0, 2.0, 4.0 or 8.0 mg/kg of the salt). Amphetamine administrations were separated by 3 days.

Results and Discussion

At low to moderate doses amphetamine produced a dose-dependent increase in the locomotor activity of both control and diabetic rats (Fig. 2). However, the diabetics show a decreased maximal response to the drug. An analysis of variance revealed a significant effect of group ($F = 20.5$; $p<0.01$) and dose ($F = 8.5$; $p<0.01$). A comparison of the two curves also suggests that the dose-response relationship for the diabetic group is shifted to the right of controls (indicating a diminished sensitivity to the drug). Note that whereas controls show a substantial increment in activity

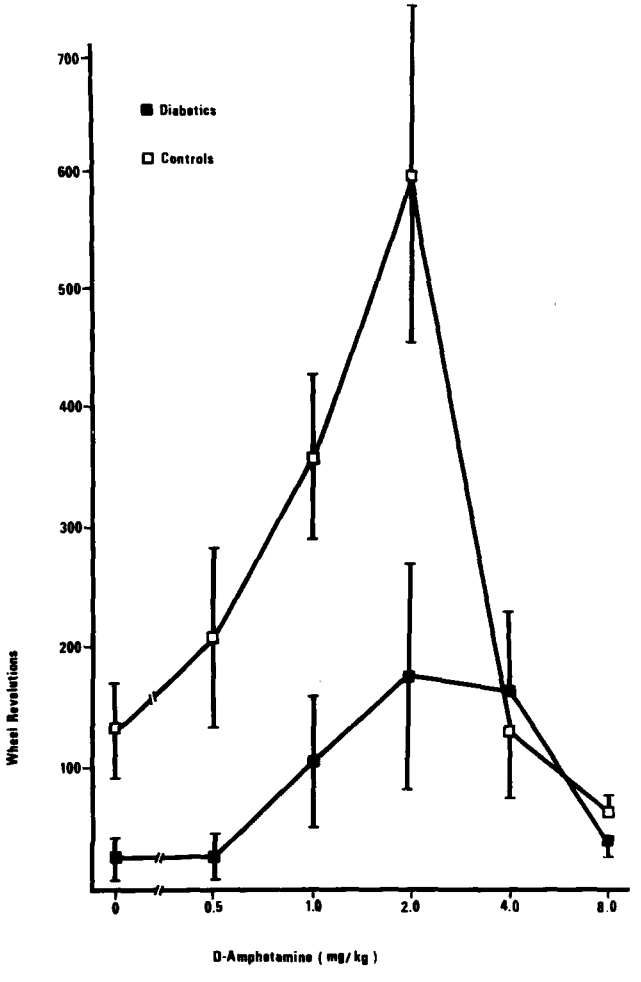

FIG. 2. Locomotor activity following d-amphetamine sulfate in control or alloxan-diabetic rats. Ordinate depicts the number of wheel revolutions in the 90 min following amphetamine administration. Mean ± SEM Scheffé tests reveal that the control and diabetics differ significantly ($p<0.025$) at the 2.0 mg/kg dose.

between 0 and 0.5 mg/kg, diabetics show no signs of increased locomotor activity with doses less than 1.0 mg/kg. Compare as well the differences between 2.0 and 4.0 mg/kg. Support for the conclusion of a shift in the dose-response curve for diabetics comes from the finding of a significant interaction ($F = 3.7$; $p<0.01$) between group and dose.

The decreased locomotor activity of both groups at higher doses is attributable to the appearance of interfering stereotyped behaviors (e.g., intense sniffing in a small area). However, it seemed to us that the stereotyped behaviors were less intense in diabetic than in control animals, an observation which prompted Experiment 3.

Despite the diminished responsiveness of the diabetic rat to the locomotor stimulant action of this drug, it is important to note that the time-response curves of the two groups following amphetamine are nearly parallel (Fig. 3). The similar shape of these two curves suggests (1) that the diminished locomotion of the diabetic rat is not due to a rapid fatiguing of its motor functions, and (2) that the

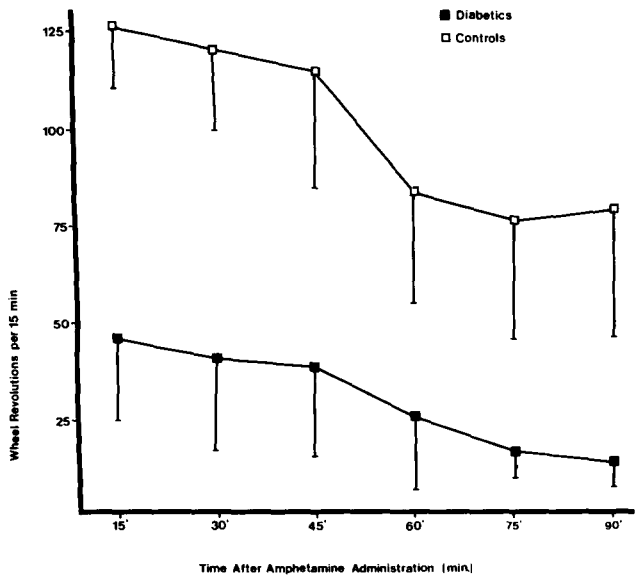

FIG. 3. Time-response curve of control and alloxan-diabetic rats to the locomotor-activity-inducing action of d-amphetamine sulfate (2 mg/kg). Ordinate depicts the number of wheel revolutions in each 15 min interval. Abscissa depicts time intervals after amphetamine administration (e.g. 15' = 0 to 15 min after amphetamine, etc.). Mean ± SEM.

diabetic state does not produce a more rapid metabolism of amphetamine, a conclusion supported as well by our previous work [18].

EXPERIMENT 3: RESISTANCE OF ALLOXAN-DIABETIC RATS TO AMPHETAMINE-INDUCED STEREOTYPED BEHAVIORS AND ITS REVERSAL WITH INSULIN

The preceeding experiments have shown that alloxan-treated diabetic rats are resistant to both the anorexic and locomotor-stimulant actions of amphetamine. The present experiment examines yet another class of behavior induced by this compound: the stereotyped behaviors (sniffing, licking, and biting) which result from administering moderate or high doses of amphetamine. In addition, the present experiment evaluates whether the behavioral response to amphetamines in alloxan-injected rats can be restored by chronic administration of insulin.

Method

Sixteen female rats were given an injection of alloxan (185 mg/kg). Thirteen were uninjected controls. All were maintained on Purina pellets and water ad lib. Two weeks later, all rats were given 2.0 mg/kg d-amphetamine sulfate (as the salt) and returned to their home cages. The rats were observed for the following 90 minutes, and their behaviors rated according to the following rating scale (modified from 29): 0 = inactivity; 1 = normal activity; 2 = increased forward locomotion; 3 = occasional sniffing over a wide area; 4 = continual sniffing over a wide area; 5 = continual sniffing restricted to a small area; 6 = intermittent licking or biting; 7 = continual licking or biting. In one of the data analyses (Fig. 4), a single behavioral rating score was determined for each rat by summing the individual scores

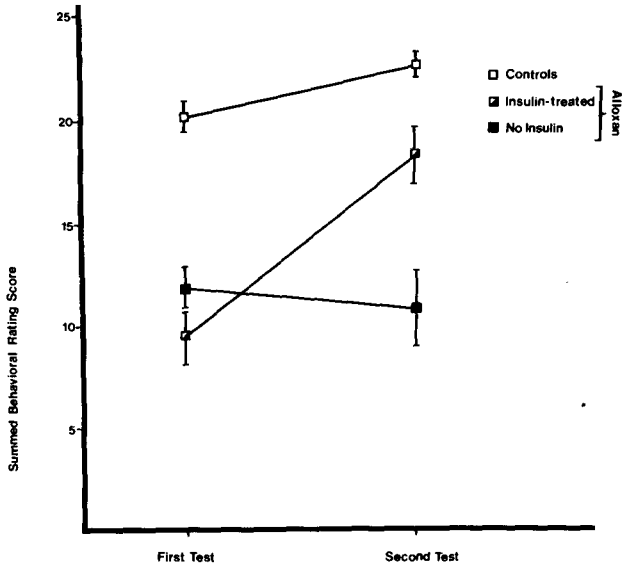

FIG. 4. Stereotyped behavior following d-amphetamine sulfate (2 mg/kg) in control rats or alloxan-diabetic rats. Between the first and second test one group of alloxan-injected rats received daily insulin treatment; the other groups were untreated. Ordinate depicts the sum of behavioral rating scores during the 90 min after amphetamine administration. Mean ± SEM.

received at each of the six 15-min intervals following amphetamine administration. After this test (First Test, Fig. 4), 8 of the alloxan-diabetic animals were given daily injections of protamine zinc insulin (Lilly, subcutaneous) for 10 days. The dose of insulin was increased from 2 IU/rat/day on the first day to 5 IU/rat/day by the fourth day. On the 4th to 10th day of insulin therapy all rats received 2 injections of 2 IU each (separated by 8 hr) during the light period of the cycle and 1 IU during the dark. Then, all rats were retested (Second Test, Fig. 4) for their response to 2 mg/kg d-amphetamine 16 hr after the last insulin injection.

Results and Discussion

As anticipated, alloxan-diabetic rats were resistant to the stereotypy-inducing affects of d-amphetamine (Figs. 4 and 5). Whereas control animals typically showed continual stereotyped sniffing over a wide area (rating of 4) at this dose of amphetamine (Fig. 5), the rats with uncorrected diabetes typically showed only increased locomotor activity (rating of 2) or occasional sniffing (rating of 3). Using these rating scores, the differences between the control group and the 2 alloxan-diabetic groups are highly significant ($p<0.001$; Fig. 4). Furthermore, if a rating of 4 or above is taken to represent true stereotyped behaviors, then significantly more of the control rats display stereotypies than do alloxan-diabetics ($\chi^2 = 15.2, p<0.001$).

The regimen of protamine zinc insulin employed induced a dramatic and significant ($p<0.001$) increase in responsiveness of the diabetic rat to d-amphetamine (Fig. 4). In contrast, the diabetic rats which did not receive insulin showed no significant ($p>0.05$) change in their behavior when retested. As depicted in Fig. 5, the alloxan-injected rats receiving insulin typically received a maximum

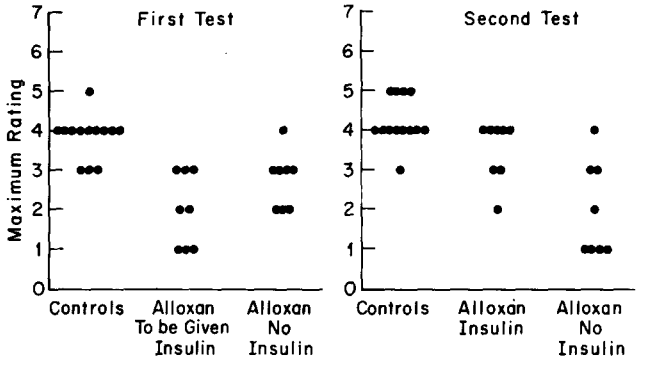

FIG. 5. Maximum rating score achieved by each individual rat during the 90 min test following administration of d-amphetamine sulfate (2.0 mg/kg). Each dot signifies the maximum rating achieved by a single rat.

rating of 4 (continual sniffing over a wide area), comparable to that observed in non-diabetic controls. Using a value of 4 or more as the criterion for stereotyped behavior, the proportion of rats in the alloxan plus insulin group displaying stereotypies does not differ from the proportion of control rats ($\chi^2 = 2.95, p>0.05$). The incidence of stereotypies among the alloxan-treated rats without insulin, however, is significantly less than in the control group ($\chi^2 = 13.73, p<0.001$).

It should be noted that control rats showed a slight but significant ($p<0.05$) increase in their behavioral rating scores when retested on the same dose of amphetamine. Previous workers have noted an increased behavioral response to this drug in normal rats with repeated administration [16]. However, the increment in behavioral response to amphetamine between the first and second tests seen among the insulin-treated group was significantly ($p<0.01$) greater than that seen among controls.

GENERAL DISCUSSION

The findings of this and our previous experiments document the existence of a robust and hitherto unreported resistance of the diabetic rat to the behavioral effects of d-amphetamine. First, the alloxan-diabetic rat appears resistant to the anorexic action of this compound, a finding which does not appear attributable simply to their increased hunger. Second, alloxan-treated animals show less locomotor activity following amphetamine. This resistance has been seen when rats are tested either in photobeam cages [18] or in activity wheels (present work). Third, they show less stereotyped sniffing behavior following the administration of this compound.

This resistance to the multiple behavioral actions of amphetamine appears due to the diabetic state of the alloxan-injected animal. When such rats are given chronic injections of protamine zinc insulin, both the anorexic [18] and stereotypy-inducing (present findings) effects of amphetamine are largely restored. In this respect, J. F. Marshall and N. E. Rowland (unpublished observations) have also observed a resistance to the locomotor-stimulant action of d-amphetamine (1.0 mg/kg) in rats made diabetic by intravenous administration of the more selective β-cell toxin, streptozotocin.

The mechanism for the diabetes-induced resistance to amphetamine's action remains unresolved, though some interesting possibilities suggest themselves. First, it seems clear that this resistance is not due to an altered accumulation of d-amphetamine in the blood or nervous system of the diabetic. Experiments utilizing ^{3}H-amphetamine have shown the accumulation of this compound in plasma and brain to be remarkably normal at 15 min and 60 min following its administration [18]. The current observation of a parallel time-response curve to amphetamine's locomotor-stimulant action in control and alloxan-treated rats further argues against the possibility of an altered metabolism of this compound in the diabetic state.

How then might the altered behavioral response be explained? A considerable body of evidence now supports the involvement of brain catecholamine-containing neurons in amphetamine's anorexic, locomotor-stimulant, and stereotypy-inducing effects. These findings point particularly to the involvement of central dopaminergic neurons. Intracerebral administration of amphetamine or of directly acting dopamine agonists, particularly when applied to regions of dopamine nerve terminals, can produce decreased food intake [17], increased locomotion [1,22] and stereotyped behaviors [6,11]. Furthermore, the anorexic, locomotor-stimulant, and stereotypy-inducing effects of amphetamine are all attenuated by the prior administration of the catecholamine synthesis inhibitor, alpha-methyl-para-tyrosine [2, 10, 26, 27, 29]. Also, prior damage to brain dopamine-containing neurons greatly reduces all of these behavioral effects of the drug [5, 6, 8, 9, 15, 21, 24].

Thus, there is a striking parallel between the diabetic rat's response to amphetamine and that of rats with pharmacologically- or lesioned-induced-depletion of brain catecholamine neurons. These similarities suggest the possibility that the diabetic rat may suffer from an alteration in central catecholamine function, a line of inquiry that we are now pursuing [19].

Although a possible alteration in the neurotransmission of central catecholamine neurons is one possible explanation for the phenomena described here, it is not the only one.

First, one might argue that the diabetic rats are simply sick, rendering them less capable of showing a behavioral response to any pharmacological treatment. While this hypothesis may account for their diminished locomotor activity and stereotyped behavior following drug treatment, it does not readily explain why these rats show more of one behavior (feeding) when given amphetamine. Nor would this hypothesis account for the fact that there is a horizontal shift of the dose response curve for amphetamine-induced locomotor activity. While a sickness interpretation cannot be refuted at the present time, our current perspective is that the diabetic rat is resistant to the actions of amphetamine, regardless of whether this resistance necessitates that it engage in more or less of any particular behavior.

Finally, amphetamine and other catecholamine agonistic compounds are known to have important effects on the intermediary metabolism of the central nervous system (e.g. inducing glycogenolysis – [7,20]). If these metabolic consequences of amphetamine administration are importantly involved in the central actions of this drug, then it seems possible that a cerebral metabolic derangement associated with the diabetic state may underlie the observed resistance to this compound. In the peripheral nerve of diabetic rats, a possible relationship between metabolic abnormalities and altered nerve function has been suggested [14]. The diabetic state results in the accumulation of insoluble sugars in the nerve. These substances, perhaps by their osmotic effect, are believed to result in a slowing of axonal conduction velocity and eventual histopathologic changes [14,23]. The clear suggestion of an altered central nervous system response to amphetamine raises the possibility that the metabolic consequences of diabetes mellitus may also alter brain function.

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