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# THE ROLE OF ADRENALS IN DIAZINON-INDUCED CHANGES IN CARBOHYDRATE METABOLISM IN RATS

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Treatment of rats with diazinon (40 mg/kg, i.p.) resulted in hyperglycaemia and depletion of glycogen from the brain and peripheral tissues two hours after administration. The activities of glycogen phosphorylase and phosphoglucomutase were significantly higher in the brain and liver; that of glucose-6-phosphatase was not altered. The activities of the glycolytic enzymes hexokinase and lactate dehydrogenase were increased only in the brain. The cholinesterase activity in the brain was reduced by treatment with diazinon. The activities of the hepatic gluconeogenic enzymes fructose 1,6-diphosphatase and phosphoenolpyruvate carboxykinase were significantly increased. The lactate level was increased in the brain and blood, whereas that of pyruvate was not changed. The activity of glucose-6-phosphate dehydrogenase was not changed to any major extent. Cholesterol and ascorbic acid contents of adrenals were depleted in diazinon-treated animals. The changes were pronounced after intraperitoneal administration of 40 mg/kg diazinon, they were slight but significant after 20 mg/kg, and absent after 10 mg/kg. Hyperglycaemia and changes in carbohydrate metabolism were abolished by adrenalectomy suggesting possible involvement of adrenals.

Diazinon, an organophosphorous compound, is commonly used in the control of agricultural and household pests. It inhibits cholinesterase activity producing central stimulatory effects of hyperexcitability, tremors and convulsions, which are related to the accumulation of acetylcholine in the central nervous system (1, 2). The compound also produces hyperglycaemia (3, 4) whose mechanism is not clear. The aim of the present study was to determine the changes in carbohydrate metabolism induced by diazinon. As the metabolism of carbohydrates is influenced by adrenals, the changes induced by diazinon in adrenalectomized rats were also determined.

## MATERIAL AND METHODS

Experimental animals were adult female albino rats, 150 ± 10 g, six months old, placed in three groups. They were maintained on a 12 h light dark cycle and had free access to food and water. They were fasted for 18 h before the experiment. The rats in Group I served as controls and were given normal saline, those in Group II were injected diazinon (10, 20 or 40 mg/kg, i.p.) and the animals in Group III were adrenalectomized. Bilateral adrenalectomy was performed under light ether anaesthesia. The adrenalectomized animals were given 1% sodium chloride in drinking water. They were treated with diazinon 10 days after adrenalectomy. The animals were decapitated two hours after treatment. Blood was collected in heparinized tubes for the estimation of glucose by the method of *Nelson* (5). The brain, liver and adrenals were dissected and weighed quickly. The glycogen content of the brain and liver was extracted according to the method of *LeBaron* (6) and estimated colorimetrically as described by *Montgomery* (7). Glycogenolytic enzymes were assayed in 1% homogenate prepared in ice-cold 0.25 M sucrose. Glycogen phosphorylase (E.C. 2.4.1.1.) and glucose-6--phosphatase (E.C. 3.1.3.9.) were assayed by the method of *Hers and Hoof* (8) and phosphoglucomutase (E.C. 2.7.5.1.) by that of *Najjar* (9). For assaying hexokinase (E.C. 2.7.1.1.) activity, the tissue was homogenized in media containing 0.15 M KCl, 0.005 M EDTA and 0.04 M $MgCl_2$. For lactate dehydrogenase (E.C. 1.1.1.27.) phosphate buffer (pH 7.4) was used. The enzymes were assayed according to the procedures of *Crane and Sols* (10) and *Kornberg* (11) respectively. Fructose 1,6 diphosphatase (E.C. 3.1.3.11.) and phosphoenolpyruvate carboxykinase (E.C. 4.1.1.49) were assayed in 1% homogenate prepared in 0.25 M sucrose by the methods of *Mendicino and Vasornely* (12) and *Philips and Berry* (13). Brain cholinesterase activity (E.C. 3.1.1.7.) was measured according to the method of *Ellman and co-workers* (14) using acetylthiocholine as substrate. Glucose-6-phosphate dehydrogenase (E.C. 1.1.1.49) activity was assayed according to the method of *Kornberg and Horacker* (15). Lactate and pyruvate levels were measured by the methods of *Barker and Summerson* (16) and of *Theodore and co-workers* (17). Adrenal ascorbic acid and cholesterol contents were estimated after *Roe and Koether* (18) and *Chiamori and Henry* (19). Statistical comparisons were made by analysis of variance followed by Duncan's multiple range and multiple F tests (20). In some comparisons t-test was also applied. The difference was considered to be significant if $P < 0.05$.

## RESULTS

The effects of diazinon on the levels of blood glucose, hepatic and cerebral glycogen and cholinesterase activity are shown in Table 1. The blood glucose level was significantly increased and that of glycogen depleted two hours after treatment with diazinon (Table 1). Maximum changes were found two hours after intraperitoneal administration of 40 mg/kg diazinon. The changes were less pronounced after treatment with 20 mg/kg diazinon, i.p. and absent after 10 mg/kg, i.p. The activities of

Table 1.

*The effect of diazinon on the levels of blood glucose, brain and liver glycogen and brain cholinesterase activity in rats. The animals were killed two hours after treatment. (Mean $\bar{X}$ 8 ± SE)*

| Rats | Treatment with diazinon (mg/kg, i.p.) | Blood glucose (μ mol/L) | Glycogen (mg/100 gm) | | Brain cholinesterase activity (μ moles of acetylthiocholine hydrolysed/min/g) |
|---|---|---|---|---|---|
| | | | Liver | Brain | |
| Group I (controls) | | 5.2 ± 0.3 | 312.8 ± 12.6 | 96.2 ± 4.5 | 20.2 ± 0.9 |
| Group II | 10 | 5.4 ± 0.2 | 317.2 ± 8.5 | 94.2 ± 2.9 | 17.6 ± 0.4 |
| | 20 | 7.6[b] ± 0.2 | 256.4[b] ± 7.5 | 80.2[b] ± 3.1 | 14.0[a] ± 0.2 |
| | 40 | 10.4[b] ± 0.2 | 201.5[b] ± 10.9 | 67.4[b] ± 3.9 | 9.1[a] ± 0.6 |
| Group III (adrenalectomized) | 40 | 5.4 ± 0.3 | 303.9 ± 11.4 | 90.1 ± 4.1 | 10.6 ± 0.8 |

[a] $P < 0.01$ as compared to control values
[b] $P < 0.01$ as compared to control values

glycogen phosphorylase and phosphoglucomutase were significantly increased both in the liver and brain while that of glucose-6-phosphatase did not change much in either tissue (Table 2). The activities of hexokinase and lactate dehydrogenase in the brain were also elevated. Glucose-6-phosphate dehydrogenase activity was not appreciably changed by treatment with diazinon (Table 3). The lactate content of the brain and blood was increased while that of pyruvate did not change a great deal (Table 4). The activities of gluconeogenic enzymes, fructose 1,6 diphosphatase and phosphoenol-pyruvate carboxykinase, were significantly increased in the liver. Fructose 1,6 diphosphatase activity was also increased in the brain (Table 5). Ascorbic acid and cholesterol contents of adrenals were depleted by treatment with diazinon (Table 6). The diazinon-induced changes in the levels of blood glucose, cerebral and hepatic glycogen (Table 1), lactate and pyruvate (Table 4) and other enzymes (Tables 2, 3 and 5) were abolished by adrenalectomy.

## DISCUSSION

The results indicate that the hyperglycaemia induced by diazinon was accompanied by depletion of glycogen in the liver and brain, by changes in the activities of glycolytic and glycogenolytic enzymes and by depletion of adrenal ascorbic acid and cholesterol.

Table 2.

*The effect of diazinon on glycogenolytic enzymes in normal and adrenalectomized rats. The animals were killed two hours after treatment. (Mean $\bar{X}$ 8 ± SE)*

| Rats | Treatment with diazinon (mg/kg, i.p.) | Glycogen phosphorylase (µmoles of $P_1$ formed /min/g tissue) | Phosphoglucomutase (µmoles of acid stable Pi formed/min/g tissue) | Glucose-6-phosphatase (µmoles of Pi liberated/min g tissue) |
|---|---|---|---|---|
| | Brain | | | |
| Group I (controls) | | 28.6 ± 1.9 | 8.1 ± 1.9 | 2.0 ± 0.2 |
| Group II | 10 | 29.6 ± 1.2 | 8.3 ± 1.2 | 2.0 ± 0.1 |
| | 20 | 33.1 ± 1.2 | 10.1[b] ± 1.0 | 2.1 ± 0.2 |
| | 40 | 39.6[b] ± 1.8 | 12.05[b] ± 1.9 | 2.1 ± 0.3 |
| Group III (adrenalectomized) | 40 | 27.0 ± 1.7 | 9.0 ± 1.8 | 2.0 ± 0.2 |
| | Liver | | | |
| Group I (controls) | | 23.5 ± 1.9 | 24.3 ± 1.0 | 5.7 ± 1.2 |
| Group II | 10 | 24.0 ± 1.2 | 25.2 ± 1.0 | 5.7 ± 1.9 |
| | 20 | 26.6[b] ± 1.1 | 27.7 ± 0.7 | 5.8 ± 0.9 |
| | 40 | 29.6[a] ± 1.8 | 31.9 ± 1.0 | 6.1 ± 1.2 |
| Group III (adrenalectomized) | 40 | 22.5 ± 1.8 | 24.0 ± 1.0 | 5.6 ± 1.0 |

[a] $P < 0.01$ as compared to control values
[b] $P < 0.01$ as compared to control values

The changes induced were maximal with the highest dose of diazinon (40 mg/kg, i.p.), slight but significant after 20 mg/kg, i.p., and absent after a dose of 10 mg/kg, i.p. It was previously reported that the cerebral glycogen content depended on the state of activity of the brain; its level diminished during activation or stimulatory states (21) and increased after treatment with barbiturates or sedatives (22, 23). Thus the depletion of glycogen (Table 1) in the brain may be related to the stimulatory effects in diazinon-treated animals, which also had a significantly low level of cerebral cholinesterase activity (Table 1). Treatment with certain organophosphorus compounds resulted in the accumulation of cyclic AMP which produces stimulatory effects and is involved in the storage of glycogen (24). It also increased the level of acetylcholine at the neuroeffector sites, inducing the release of catecholamines (25). These changes may have activated glycogen phosphorylase (26), which according to our results was significantly increased in the brain and liver of diazinon-treated animals (Table 2). The activity of phosphoglucomutase, another glycogenolytic enzyme, was also increased in

Table 3.

*The effect of diazinon on certain glycolytic enzymes and glucose-6-phosphate dehydrogenase activity in normal and adrenalectomized rats. The animals were killed two hours after treatment. (Mean $\bar{X}$ 8 ± SE)*

| Rats | Treatment with diazinon (mg/kg, i.p.) | Hexokines (μmoles of glucose phosporylated/min/mg) | Lactate dehydrogenase (μmoles of NADH oxidized /min/mg protein) | Glucose-6-phosphate dehydrogenase (μmoles of NADP reduced /min/mg protein |
|---|---|---|---|---|
| | Brain | | | |
| Group I (controls) | | 3.8 ± 0.4 | 254.4 ± 10.0 | 13.1 ± 2.4 |
| Group II | 10 | 3.9 ± 0.3 | 247.3 ± 8.5 | 12.9 ± 1.8 |
| | 20 | 4.4 ± 0.2[b] | 270.2 ± 7.91[b] | 13.2 ± 1.6 |
| | 40 | 4.9 ± 0.4[a] | 285.7 ± 12.8[a] | 12.7 ± 2.2 |
| Group III (adrenalectomized) | 40 | 3.8 ± 0.4 | 248.4 ± 11.3 | 12.2 ± 2.3 |
| | Liver | | | |
| Group I (controls) | | 1.3 ± 0.2 | 603.8 ± 14.1 | 58.3 ± 4.9 |
| Group II | 10 | 1.3 ± 0.2 | 605.7 ± 10.6 | 54.2 ± 3.1 |
| | 20 | 1.4 ± 0.1 | 607.5 ± 8.5 | 55.0 ± 2.9 |
| | 40 | 1.4 ± 0.2 | 609.6 ± 13.5 | 53.6 ± 3.9 |
| Group III (adrenalectomized) | 40 | 1.3 ± 0.3 | 601.7 ± 15.61 | 56.7 ± 4.0 |

[a] $P < 0.01$ as compared to control values
[b] $P < 0.05$ as compared to control values

diazinon-treated animals (Table 2) suggesting greater formation of glucose-6-phosphate from glucose-1-phosphate. Glucose-6-phosphatase activity, the enzyme which catalyzes the final step of glycogenolysis, was not significantly changed (Table 2). The activity of hexokinase, an important enzyme of the glycolytic pathway was increased (Table 2) suggesting enhanced formation of glucose-6-phosphate from glucose which is the main source of energy for the brain (27) and is actively metabolized during stimulatory states, tremors and convulsions (28); in the liver the hexokinase activity was not significantly changed suggesting that the demand for glucose was not increased in the hepatic tissue of diazinon-treated animals. The activity of cerebral lactate dehydrogenase was slightly but significantly increased (Table 3). It was previously reported that organophosphorus compounds inhibited the respiratory enzymes and reduced oxygen uptake *in vitro* as well as *in vivo* (1). These changes favour anaerobic glycolysis in diazinon-treated animals. This is in agreement with our finding that the level of lactate was increased in

Table 4.

*The effect of diazinon on the levels of brain and blood pyruvic and lactic acids in rats. The animals were killed two hours after treatment. (Mean $\bar{X}$ 8 ± SE)*

| Rats | Treatment with diazion (mg/kg, i.p.) | Brain | | Blood | |
|---|---|---|---|---|---|
| | | Pyruvic acid (μ mole/kg) mean ± S.E. | Lacid acid (μ mole/kg) mean ± S.E. | Pyruvic acid (μ mole/kg) mean ± S.E. | Lacid acid (μ mole/kg) mean ± S.E. |
| Group I (controls) | | 0.21 ± 0.06 | 2.36 ± 0.20 | 0.32 ± 0.07 | 1.41 ± 0.19 |
| Group II | 10 | 0.19 ± 0.03 | 2.33 ± 0.17 | 0.33 ± 0.05 | 1.3 ± 0.10 |
| | 20 | 0.22 ± 0.05 | 3.01[b] ± 0.22 | 0.35 ± 0.04 | 1.82[b] ± 0.14 |
| | 40 | 0.24 ± 0.08 | 3.88[a] ± 0.26 | 0.34 ± 0.06 | 2.23[a] ± 0.20 |
| Group III (adrenalectomized) | 40 | 0.20 ± 0.05 | 2.60 ± 0.23 | 0.31 ± 0.06 | 1.43 ± 0.18 |

[a] $P < 0.01$ as compared to control values
[b] $P < 0.01$ as compared to control values

Table 5.

*The effect of diazinon on gluconeogenic enzyme activities in the liver and brain tissues of normal and adrenalectomized rats. The animals were killed two hours after treatment. (Mean $\bar{X}$ 8 ± SE)*

| Rats | Treatment with diazion (mg/kg, i.p.) | Fructose 1, 6-diphosphatase (μ moles of Pi formed/min/g tissue) | | Phospoenolopyruvate carboxy kinase (μ moles of phospoenolpyruvate formed/min/g tissue) | |
|---|---|---|---|---|---|
| | | Liver mean ± S.E.s | Brain mean ± S.E. | Liver mean ± S.E.s | Brain mean ± S.E. |
| Group I (controls) | | 7.9 ± 0.08 | 2.9 ± 0.2 | 18.8 ± 0.09 | 4.6 ± 0.8 |
| Group II | 10 | 7.6 ± 0.06 | 2.1 ± 0.1 | 16.9 ± 0.07 | 4.7 ± 0.4 |
| | 20 | 9.5[b] ± 0.04 | 2.5 ± 0.1 | 18.4 ± 0.02 | 4.8 ± 0.8 |
| | 40 | 11.0[a] ± 0.07 | 2.8 ± 0.2 | 20.5 ± 0.09 | 4.9 ± 0.8 |
| 2 | | | | | |
| Group III (adrenalectomized) | 40 | 7.5 ± 0.07 | 2.0[a] ± 0.7 | 16.4 ± 0.08 | 4.5 ± 0.8 |

[a] $P < 0.01$ as compared to control values
[b] $P < 0.05$ as compared to control values

Table 6.

*The effect of diazinon on ascorbic acid and cholesterol contents of adrenals in rats. The animals were killed two hours after treatment. (Mean $\bar{X}$ 8 ± SE)*

| Rats | Treatment with diazinon (mg/kg, i.p.) | Cholesterol (mg/g tissue) mean ± S.E. | Ascorbic acid (mg/g tissue) mean ± S.E. |
|---|---|---|---|
| Group I (controls) | | 65.0 ± 0.8 | 4.2 ± 0.2 |
| Group II | 10 | 66.9 ± 2.7 | 4.4 ± 0.1 |
| | 20 | 55.1[b] ± 2.0 | 3.3[b] ± 0.1 |
| | 40 | 43.3[b] ± 3.1 | 2.7[b] ± 0.2 |

[a] P < 0.01 as compared to control values
[b] P < 0.02 as compared to control values

the brain and blood while that of pyruvate was not significantly changed (Table 4). As the activity of glucose-6-phosphate dehydrogenase (Table 3)) was not greatly changed in diazinon-treated animals, it seems that the direct oxidation of glucose through the hexose monophosphate pathway was not altered in these animals.

The results further indicate an increase in the activities of gluconeogenic enzymes, fructose 1,6-diphosphatase and phosphoenolpyruvate carboxynase, in the liver (Table 5), which is the main site of gluconeogenesis in the body (29). It was previously reported that organophosphorus compounds by their anticholinesterase action, interfered with neuroregulatory pathways in the central nervous system which controls the secretory activity of the anterior pituitary (30) resulting in the release of ACTH (31). Further, ACTH has also been reported to stimulate the adrenals to secrete corticosteroids (32). The increased activities of the two hepatic gluconeogenic enzymes in diazinon-treated animals may be related to the central or peripheral effect of diazinon inhibiting cholinesterase at both sites. Support for the involvement of adrenals is also gained from the finding that treatment with diazinon resulted in depletion of ascorbic acid and cholesterol from the adrenals (Table 6). Adrenalectomy also prevented changes in the activities of gluconeogenic enzymes in diazinon-treated animals (Table 5). It is of interest to note that adrenalectomy, which modified changes in enzymes involved in carbohydrate metabolism, failed to modify changes in the level of cerebral cholinesterase activity in diazinon-treated animals. Cholinesterase is widely distributed in blood, different regions of the brain and various cholinergic synapses including neuroeffector sites of the adrenal medulla (33). By inhibiting cholinesterase diazinon may induce (a) peripheral effects resulting in the release of catecholamines, and (b) central effects due to accumulation of acetylcholine in the brain (34) leading to increased secretion of catecholamines (35). Thus diazinon may act by peripheral as well as by central mechanisms. A direct effect of diazinon is also possible owing to depletion of ascorbic acid and cholesterol from the adrenals (Table 6).

As changes in the level of blood glucose, glycogen (Table 1) and related enzymes were accompanied by depletion of cholesterol and ascorbic acid (Table 6) from adrenals and as the induced changes in the activities of glycolytic, glycogenolytic and gluconeogenic enzymes were abolished by adrenalectomy (Tables 2 – 5), it seems that adrenal glands may have been partly involved in the production of changes in carbohydrate metabolism mediated through the central or peripheral effect of diazinon inhibiting cholinesterase at both sites.

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*Sažetak*

## ULOGA ADRENALNIH ŽLIJEZDA U NASTANKU PROMJENA U METABOLIZMU UGLJIKOHIDRATA IZAZVANIH DIAZINONOM U ŠTAKORA

U štakora koji su dobivali diazinon (40 mg/kg) intraperitonealno dva sata nakon primjene utvrđena je hiperglikemija i smanjenje nivoa glikogena u tkivima mozga i živaca. Aktivnosti glikogen fosforilaze i fosfoglukomutaze u mozgu i jetri bile su značajno više, dok se aktivnost glukoza-6-fosfataze nije promijenila. Glikolitski enzimi heksokinaza i laktat dehidrogenaza imali

su povišenu aktivnost samo u mozgu. Tretman diazinonom doveo je do smanjene aktivnosti kolinesteraze u mozgu. Aktivnosti glukoneogenih enzima jetre fruktoza 1,6-difosfataze i fosfoenolpiruvatne karboksikinaze značajno su porasle. Nivo laktata bio je povišen u mozgu i krvi, dok je koncentracija piruvata ostala nepromijenjena. Aktivnost glukoza-6-fosfatne dehidrogenaze nije se bitno promijenila. Sadržaj kolesterola i askorbinske kiseline u nadbubrežnim žlijezdama bio je niži u životinja koje su primale diazinon. Promjene su bile najizraženije nakon doze od 40 mg/kg diazinona, male ali značajne nakon doze od 20 mg/kg, a nije ih bilo nakon doze od 10 mg/kg. Hiperglikemija i promjene u metabolizmu ugljikohidrata bile su spriječene adrenalektomijom što ukazuje na moguću ulogu nadbubrežnih žlijezda u biokemijskim promjenama izazvanima diazinonom.

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