# Metabolic Effects of Sodium Dichloroacetate in Normal and Diabetic Dogs

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**SUMMARY**

**The effects of acute and chronic administration of sodium dichloroacetate (DCA) were studied in the normal and diabetic dog. In the normal dog, a single oral injection of DCA (150 mg/kg) provoked a rapid decrease of the lactate, pyruvate, and triglyceride concentrations and a progressive decrease of blood glucose. These effects lasted longer than 24 h.**

**In the alloxan-diabetic dog deprived of insulin for 72 h, DCA induced a decrease of blood glucose, lactate, and pyruvate concentrations as well as of glucosuria. In these ketotic animals, the plasma lipid compounds and the blood and urinary ketone bodies were not significantly changed by DCA.**

**In the normal dog, the chronic administration of DCA (150 mg/kg daily for 7 days) provoked a decrease in blood glucose, lactate, pyruvate, and oxaloacetate concentrations, which returned to starting values only within 2 to 5 days after the end of the treatment, depending on the compounds studied. A decrease of cholesterol was also noted. During the chronic administration of DCA, blood β-hydroxybutyrate and acetoacetate concentrations strongly increased.**

**When treated with insulin alone, the alloxan-diabetic dogs had a high blood glucose concentration; the blood lactate, pyruvate, and oxaloacetate concentrations did not differ significantly from those of the normal animals, however. In these diabetic dogs, the lipid compounds and, particularly, the ketone compounds were increased. The addition of DCA (75 mg/kg daily for 7 days) provoked a drop in blood lactate, pyruvate, and oxaloacetate levels, and a reduction of blood glucose and plasma cholesterol, triglyceride, and total lipids was also noted. Blood β-hydroxybutyrate and acetoacetate concentrations, which were already high at the start, were not affected when DCA was associated to insulin. This addition of DCA provoked a rapid and marked reduction in glucosuria, which was concomitant with an increase in urinary β-hydroxybutyrate and acetone.**

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The hypoglycemic activity of di-isopropylammonium dichloroacetate (DIPA) was observed as early as 1962 by Lorini and Ciman[1] in the alloxan-diabetic but not in the normal, fed rat. At the same time, Vailati and Rabassini[2] described a short-term utilization of this agent in the treatment of human diabetes mellitus.

Stacpoole and Felts[3,4] demonstrated that dichloroacetate was the active component of the molecule. From the work of Mac Allister et al.,[5] dichloroacetate (DCA) is known to stimulate pyruvate dehydrogenase, and, according to Whitehouse et al.,[6] this effect may be explained by the inhibition of the action of pyruvate dehydrogenase kinase. It is probable that this mechanism accounts for the beneficial action of DCA observed in experimental hyperlactatemia.[7–9]

Several authors[10–13] recently studied the effects of DCA in the experimental or clinical diabetes mellitus and observed a hypoglycemic effect. Moreover, Searle et al.[14] demonstrated that the chronic administration of DCA in depancreatized dogs provoked a significant elevation of glucose oxidation. This result is consistent with the effects observed by Stacpoole and Felts[3] in incubated tissues. However, the effects of this drug on lipid metabolism, especially its influence on the formation of ketone bodies, is not well elucidated.

The aim of this work was to study in vivo in the normal and diabetic dog the action of DCA on carbohydrate and lipid metabolism.

## MATERIALS AND METHODS

### GENERAL EXPERIMENTAL CONDITIONS

Our experiments were carried out on the conscious dog. Dichloroacetic acid was obtained from Koch Light Laboratories (Colubrook, Bucks, England). It was diluted in distilled water at 6% and adjusted to pH 7 with NaOH. Two experimental patterns were used.

**Acute experiments.** A single dose of 150 mg/kg DCA was administered by gastric intubation.

*Normal mongrel dogs*, weighing 14 to 18 kg, were fasted



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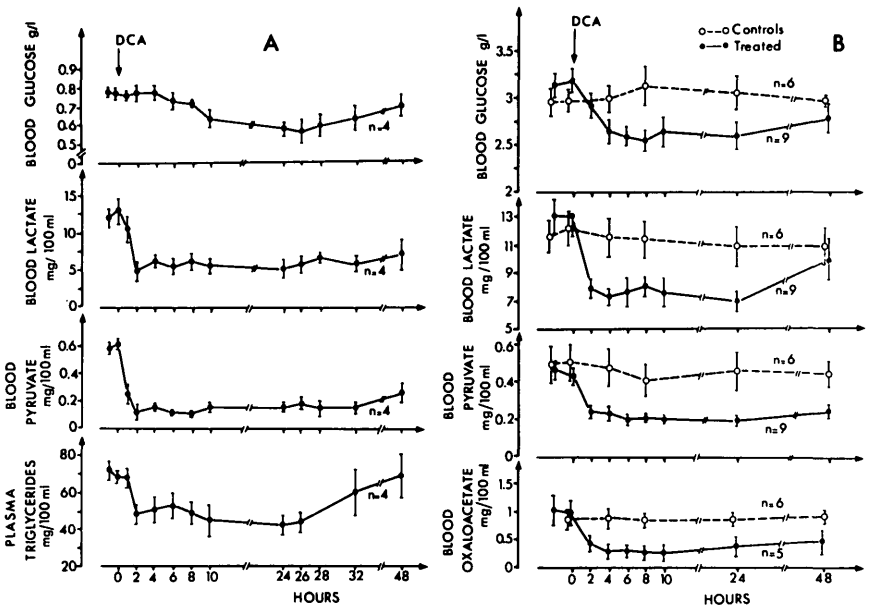


**FIGURE 1. (A) Effects of a single oral DCA injection (150 mg/kg) in normal dogs on blood glucose, lactate, pyruvate, and plasma triglyceride concentrations (mean ± SEM). (B) Effects of a single oral DCA injection (150 mg/kg) in ketotic, alloxan-diabetic dogs on blood glucose, lactate, pyruvate, and oxaloacetate levels (mean ± SEM). Ketotic, alloxan-diabetic dogs that did not receive DCA are the controls.**

for 18 h before the experiment. However, as the experiment lasted for 48 h, the animals were fed 10 and 32 h after the intake of DCA.

*Diabetic dogs.* Diabetes was produced in mongrel dogs, weighing 12 to 16 kg, by intravenous injection of 50 mg/kg alloxan. At the time of experiment, the animals were diabetic for at least 2 mo and were kept in cages. Insulin was withdrawn 72 h before the start of the experiment. The usual meat diet was maintained throughout the experiment (30 g meat per kilogram per day). Fifteen diabetic dogs were divided into two groups: nine received an intragastric injection of 150 mg/kg DCA, and six were submitted to a gastric intubation of 20 ml sodium chloride at 9‰.

**Chronic experiments.** DCA was administered daily during 7 days. *Normal dogs* received an oral dose of 150 mg/kg per day with the morning meal. *Diabetic dogs* received, on one hand, insulin subcutaneously at the same dose as the preceding days, and, on the other hand, DCA at an oral dose of 75 mg/kg daily with the morning meal.

## METHODS

Blood was sampled from the jugular vein before and after the administration of DCA. In acute experiments, dogs that received a single dose were observed during 48 h. In chronic experiments, fasting venous blood was taken every morning, i.e., 18 h after the last meal.

Blood glucose values were recorded with a Technicon AutoAnalyzer by use of the potassium cyanide procedure for hemolyzed blood.[15] Blood lactate and pyruvate levels were determined in whole blood according to the enzymatic methods of Hohorst[16] and Czock and Lamprecht,[17] respectively.

Plasma triglyceride, cholesterol, and total lipid were determined by the enzymatic methods of Wahlefield,[18] Watson,[19] and Zöllner and Kirsch.[20] Using other enzymatic methods, we were able to determine β-hydroxybutyrate concentrations[21] and those of oxaloacetate and acetoacetate[22] in whole blood.

Glucosuria and urinary β-hydroxybutyrate and acetone were also assayed.[23]

**Statistical methods.** In acute experiments, Student's *t* test was used to determine statistical significance. In chronic experiments, data from each group of animals (normal and diabetic dogs) were submitted to analysis of variance. The comparisons were made using F test between the set of values obtained before DCA treatment and the set of values obtained during the treatment.

## RESULTS

### ACUTE EXPERIMENTS

**Normal dogs.** Blood lactate rapidly decreased after DCA administration and reached 35% of the starting value within 2 h (Figure 1 A). Blood lactate concentration remained low during the 48 h of the experiments. Blood pyruvate level decreased still more rapidly; this important decrease (−73%) lasted throughout the 48 h of the experiments. The calculated ratio lactate:pyruvate, which rose from the first hour after the administration of the drug, showed that DCA acted more rapidly and more strongly on the pyruvate than on the lactate concentration.

Blood glucose was not altered during the first 4 h after DCA ingestion, then it progressively decreased and became significantly different from the starting values from the 24th to the 28th h ($P < 0.01$ at 24th and 26th h, $P < 0.05$ at 28th h). Then glycemia returned towards initial values.

Plasma triglyceride level was decreased by DCA; this appeared clearly 2 h after intragastric administration. This reduction in triglyceride level persisted and reached its maximum at the 24th h (−37.7%).

**Diabetic dogs.** Figure 1 B shows that glycemia of DCA-treated diabetic dogs decreased from the 2nd h after the administration of the drug. This decrease became significant in comparison with the control animals from the 4th h ($0.05 > P > 0.02$). The hypoglycemic effect, which reached a maximum of −20% compared to the starting values, persisted longer than 24 h; 48 h after the intake of DCA, blood glucose levels of the treated animals were not significantly different from those of the control diabetic animals. Blood lactate level markedly decreased two hours after DCA administration. This decrease (maximum −42.3%)

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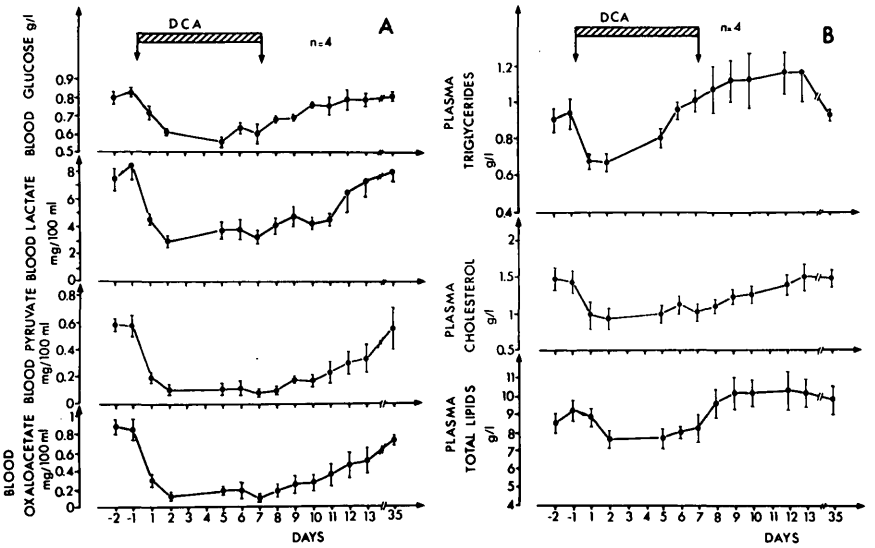



**FIGURE 2. Effect of chronic administration of DCA (150 mg/kg daily for 7 days) in normal dogs on (A) blood glucose, lactate, pyruvate, and oxaloacetate concentrations (mean ± SEM) and (B) plasma lipid compounds (triglycerides, cholesterol, and total lipids) (mean ± SEM).**

persisted at least 24 h. Blood pyruvate as well decreased very rapidly and markedly under the effect of DCA. The lowest value, 0.20 mg/100 ml of blood, was reached from the 6th h and lasted throughout the 48 h of the experiment.

DCA also provoked a decrease in blood oxaloacetate levels, which appeared from the 2nd h after the administration of the drug and persisted during the 48 h of the experiment.

As for plasma lipid compounds (triglycerides, cholesterol, and total lipids) and blood ketone bodies (β-hydroxybutyrate and acetoacetate), which were high in both series at the start of the experiment, the administration of DCA did not significantly modify the values as compared with those of the controls.

As for the action of DCA on urinary compounds, this drug did not alter the elevated acetone and β-hydroxybutyrate levels in these animals. However, the drug induced a marked decrease of glucosuria which dropped from 73.5 ± 15 g/24 h, on the average, to 24 ± 5 g/24 h ($0.02 > P > 0.01$); this decrease persisted for 48 h.

CHRONIC EXPERIMENTS

**Normal dogs.** Each dog was given DCA orally at the dose of 150 mg/kg daily during 7 days.

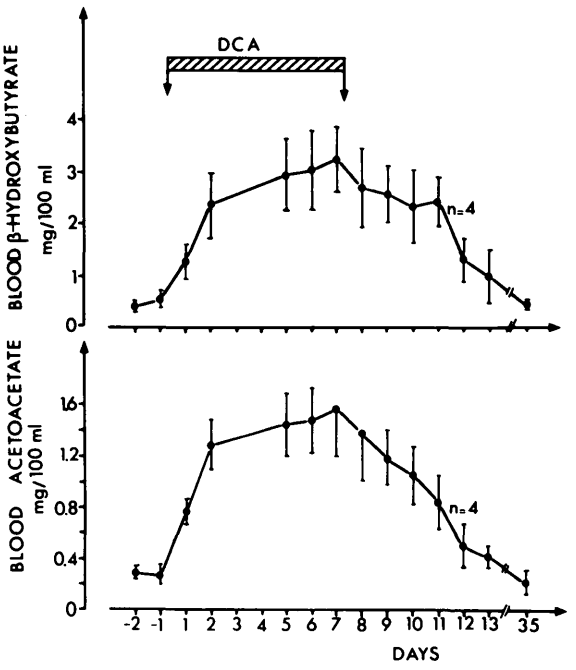
Blood glucose (Figure 2 A) decreased 24 h after the first administration. It continued to decrease the following days. During DCA administration, blood glucose levels remained significantly lower than the values recorded before DCA ($P < 0.001$). This blood glucose lowering persisted 2 days after the end of the treatment. DCA provoked a rapid fall in blood lactate and pyruvate levels. Lactatemia, which showed a marked decrease 24 h after the first administration, fell to −64% the second day of treatment. This fall persisted for 4 days after stopping the treatment. Pyruvemia showed a parallel evolution. The marked decrease (−80%) persisted also after the end of the treatment, and the initial value was not yet reached 6 days after the end of treatment. Blood oxaloacetate levels showed the same evolution as pyruvates (80% decrease).

As for lipid compounds (Figure 2 B), the daily administration of DCA provoked a decrease of most of them. Total plasma cholesterol was clearly reduced ($P < 0.001$), the initial value being reached only 5 days after the end of the treatment. Plasma total lipid and triglyceride concentrations did not decrease significantly.

Figure 3 shows that the administration of DCA (150 mg/kg daily) provoked a rapid and strong increase in blood β-hydroxybutyrate and acetoacetate concentrations, and these remained high throughout the treatment. After stopping the treatment, β-hydroxybutyrate and acetoacetate concentrations returned progressively to basal values, which were reached only the 6th day after discontinuation of treatment. In these normal animals, the urine did not contain ketone bodies.

**Diabetic dogs.** Three diabetic dogs received two subcutaneous injections of insulin per day; the doses were chosen so that the animals presented a strong glucosuria and were mildly ketonuric. After a 7-day control period, the insulin treatment was maintained at the same doses, in

**FIGURE 3. Effects of chronic administration of DCA (150 mg/kg daily for 7 days) in normal dogs on blood β-hydroxybutyrate and acetoacetate concentrations (mean ± SEM).**

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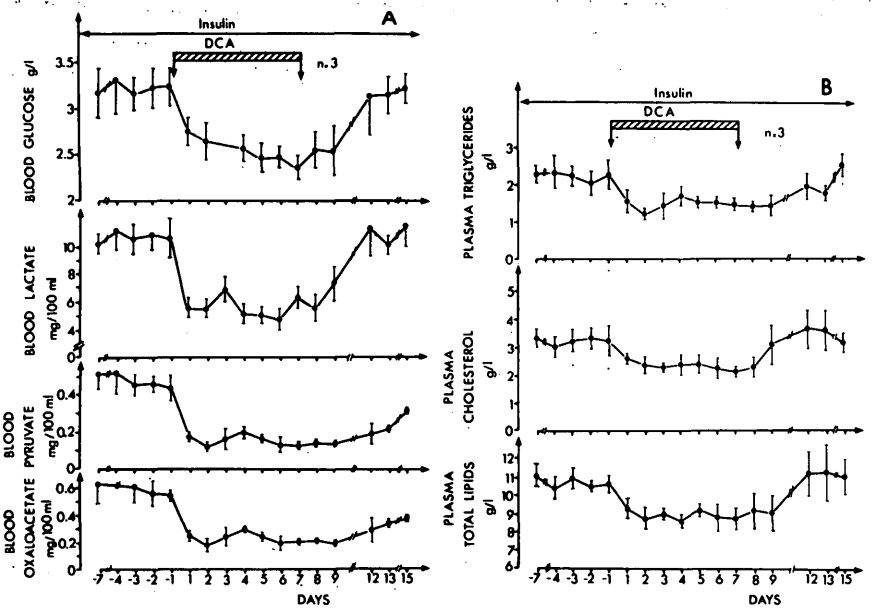


**FIGURE 4. In alloxan-diabetic dogs, effects of chronic administration of DCA (75 mg/kg daily for 7 days) added to the insulin treatment on (A) blood glucose, lactate, pyruvate, and oxaloacetate levels (mean ± SEM) and (B) plasma lipid compounds (triglycerides, cholesterol, and total lipids) (mean ± SEM).**

combination with the oral administration of DCA (75 mg/kg daily) during 7 days.

Blood glucose concentration significantly decreased during DCA administration ($P < 0.001$). This decrease in glycemia lasted 2 days after stopping DCA administration; afterwards blood glucose concentration returned to the values recorded at the beginning of the experiment. DCA provoked a rapid and parallel fall in blood lactate, pyruvate, and oxaloacetate concentrations. This effect also persisted at least 2 days after stopping the drug.

The adjunction of DCA with insulin injections resulted in a significant reduction of triglyceride ($P < 0.001$), cholesterol ($P < 0.001$), and total lipid ($P < 0.001$) values (Figure 4 B).

Finally, blood β-hydroxybutyrate and acetoacetate concentrations (Table 1), which were already high at the start of our experimental conditions, were not affected when DCA was added to insulin.

This addition of DCA to insulin provoked a rapid and marked reduction in glucosuria (Figure 5). Before DCA intake, glucosuria averaged 75.6 g/24 h, and amounted to only 22.6 g/24 h the last day of combined treatment. This decrease in glucosuria was concomitant with an increase in urinary β-hydroxybutyrate and acetone.

## DISCUSSION

From all our findings, it results that DCA lowers the blood glucose concentration and markedly reduces those of blood lactate, pyruvate, and oxaloacetate. These effects appear after a single administration of DCA, as well as during chronic treatment, in normal and diabetic dogs. The long-lasting effect of the drug must be pointed out; its effect persists for from 24 to 48 h after a single administration; after 7 days of chronic treatment, the effects can be observed during 4 to 6 days after cessation of the administration of the drug. The action of DCA on carbohydrate metabolites may be ascribed to an increased utilization of pyruvate through activation of the pyruvate dehydrogenase.[5] This increased pyruvate utilization results in a rapid decrease of lactate levels, which leads to a reduction of gluconeogenesis from this substrate as suggested by certain authors either in the liver[13,24,25,27] or in the kidney[26] or in skeletal muscle.[28]

Recently, Pegorier et al.[29] reported that the hypoglycemia induced by DCA in the suckling newborn rat was completely reversed by subcutaneous injections of exogenous gluconeogenic precursors. On the other hand, Demaugre et al.[30] demonstrated that DCA is metabolized to oxalate, which inhibits pyruvate carboxylase, in rat liver cells. For these authors, oxalate appears to be responsible for the inhibition of gluconeogenesis by DCA at the level of pyruvate carboxylation. In our own experiments, blood oxaloacetate level is decreased by DCA, which is consistent with the above mentioned findings.

The results concerning ketone bodies are different, depending on our experimental conditions. After a single

TABLE 1
Effects of chronic DCA administration added to insulin treatment on blood β-hydroxybutyrate and acetoacetate concentrations (mean ± SEM) in alloxan-diabetic dogs

| Days | −4 | −3 | −2 | −1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Insulin treatment | | | | | | | | | | | | | |
| | | | | | DCA treatment | | | | | | | | | |
| β-hydroxybutyrate mg/dl (n = 3) | 6.4 ± 2.6 | 6.1 ± 2.5 | 7.3 ± 2.48 | 10.1 ± 1.9 | 10.2 ± 2.8 | 10.2 ± 2 | 7.5 ± 1.6 | 9.7 ± 2.8 | 7 ± 1.3 | 6.4 ± 0.9 | 9 ± 0.7 | 11.9 ± 1.4 | 10.06 ± 2.6 | 12.3 ± 2.9 |
| Acetoacetate mg/dl (n = 3) | 2.74 ± 0.58 | 2.62 ± 0.32 | 2.80 ± 0.44 | 3.3 ± 0.45 | 3.49 ± 0.5 | 3.67 ± 0.5 | 3.44 ± 0.5 | 3.15 ± 0.3 | 3.15 ± 0.3 | 2.75 ± 0.22 | 3.47 ± 0.38 | 3.73 ± 0.47 | 3.28 ± 0.34 | 3.53 ± 0.41 |



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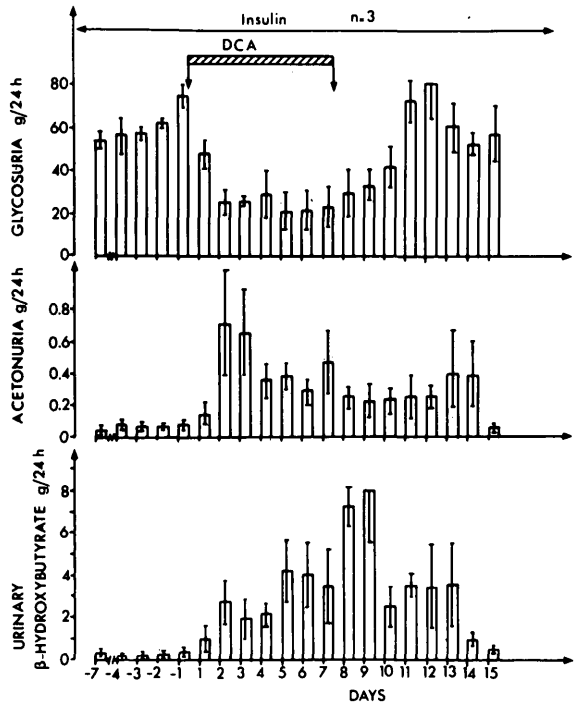


**FIGURE 5. In alloxan-diabetic dogs, effects of chronic administration of DCA (75 mg/kg daily for 7 days) added to the insulin treatment on glucosuria, acetonuria, and urinary β-hydroxybutyrate (mean ± SEM).**

DCA injection in the diabetic ketotic dog, no noticeable change in ketone bodies can be observed when compared with those in the controls. During the chronic treatment in the normal dog, DCA clearly increased blood ketone bodies, but we did not observe any appearance of ketone bodies in urine. This suggests there is a renal threshold for ketone bodies. In the diabetic dog already treated by insulin at a low dose, the addition of DCA increases urinary β-hydroxybutyrate and acetoacetate without any increase of these compounds in the blood. The blood concentration of these compounds is already high in these animals, however, even before treatment with DCA. The increase in elimination of ketone bodies with DCA suggests that this agent could interfere with tubular reabsorption of ketone bodies. This hypothesis is consistent with the results of Halestrap[31] concerning the transport of Cl-monocarboxylate on the monocarboxylate carrier. The increase in ketone bodies produced by DCA could be secondary to an enhanced hepatic acetyl-CoA formation[27] without concomitant increase of Krebs cycle rate. So, Goodman[28] has shown that DCA did not change the content of ATP in perfused skeletal muscle.

As to lipid metabolites, DCA decreases plasma cholesterol and, to a lesser extent, total lipids and triglycerides. The mechanism by which DCA provokes this decrease in plasma lipid compounds is not yet elucidated. Studies performed in animals[12] as well as in man[13] have already shown that DCA provokes a decrease in plasma triglyceride and cholesterol concentrations. Our results are consistent with these studies. Stacpoole et al.[13] suggest that this could be due to a stimulation of the triglyceride oxidation by the liver to ketones. These authors report that the decrease in plasma cholesterol could be secondary to a decrease in plasma very-low-density lipoproteins (VLDL).

Our results demonstrate the blood glucose- and lipid-lowering effect of DCA in both the normal and diabetic dog. In the diabetic dog, the hypoglycemic effect of DCA and that of insulin are additive. However, in our experimental conditions, we observed an increase in the formation of ketone bodies. Further study is needed to investigate whether it is possible to maintain the beneficial effects of DCA while eliminating this disadvantage and, thus, to improve the effects of insulin treatment.

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