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Frederick E. Samson Jr., … , Nancy Dahl, Dennis R. Dahl

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Research Article



# A STUDY ON THE NARCOTIC ACTION OF THE SHORT CHAIN FATTY ACIDS [1]

By FREDERICK E. SAMSON, JR., NANCY DAHL, AND DENNIS R. DAHL

*(From the Department of Physiology, University of Kansas, Lawrence, Kan.)*

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That the short chain fatty acids have an inhibitory action on many metabolic reactions has been shown in baker's yeast (1), bacteria (2–4), fungi (5), cell-free yeast extracts (1), and mammalian muscle (6). However, the effects of the short chain fatty acids on "intact" animals have not been studied in similar detail, except for a few studies on the toxicity of butyrate (7), β-hydroxybutyrate (8, 9), acetone (10) and acetoacetate (11). The present work is a study of the narcotic action of the neutralized salts of the short chain fatty acids upon "intact" rats.

## METHODS

Solutions of the fatty acid salts were prepared daily by adding a weighed amount of the acid (Fisher Scientific Co.) to distilled water and neutralizing it to a pH of 7.4 with 20 per cent w/v NaOH. The pH was determined with a glass electrode pH meter while air bubbled through the solution to insure adequate mixing. In this connection, pH determinations are subject to error because these acids tend to form two phase systems and colloidal gels. In the present experiments care was taken to neutralize all the free fatty acid and only homogeneous preparations were used. The concentration of the fatty acid anion is specified in the individual cases. The β-hydroxybutyrate was purchased as the sodium salt (Nutritional Biochemical Corp.) and solutions were prepared by dissolving a weighed amount in distilled water and bringing it to a pH of 7.4.

The rats used in these experiments were females from a Sprague-Dawley strain maintained on Nutrena® dog food nuggets and weighing between 50 and 200 grams. They were fasted 24 hours before experimentation and weighed immediately prior to the fatty acid injection. For species comparisons, mice, guinea pigs, dogs, chicks and frogs were used; however, detailed data were collected only with rats.

Nephrectomized rats were prepared according to the directions of Farris and Griffith (12). With the animal under ether anesthesia a dorsal midline incision was made, the renal connections isolated and tied off at the hilum, then the kidney excised. With the operation concluded, the incision was closed by two or three skin sutures and the area sealed with collodion. Rats were made alloxan-diabetic by a tail vein injection of alloxan monohydrate (Nutritional Biochemical Corp.), 40 mg. per Kg. body weight. Two weeks later, the animals were fasted 24 hours and then urine samples collected for glucose analysis. Only those rats with glucose in the urine greater than 1 per cent were considered alloxan-diabetic.

To determine whether or not an animal was conscious the animal was placed on its back at one minute intervals after the fatty acid solution was injected. If it did not right itself within ten seconds, it was judged unconscious. With most animals, and rats in particular, this gives a reproducible end point.

Urine analyses for glucose and acetone were carried out with commercially obtained tablets (Ames Co.). The determination of the fatty acids in the urine was done chromatographically (13).

## RESULTS AND DISCUSSION

Intravenous or intraperitoneal injection of the sodium salts of the short chain fatty acids produces unconsciousness in rats, frogs, chicks, mice, dogs and guinea pigs. The effect of various amounts and concentrations of the short chain fatty acids given intraperitoneally in rats is presented in Table I. As can be seen, unconsciousness occurs in two to forty minutes after injection and may persist for as long as an hour. The amount of fatty acid anion which will produce unconsciousness in 50 per cent of a sample of rats ($E_{50}$) was determined by plotting the per cent of each group of animals that lost consciousness against the amount injected and then selecting the amount which corresponded to 50 per cent (14).

There is a definite relationship between the amount of the fatty acid which will produce unconsciousness and the carbon chain length of the compound. As might be expected, the $E_{50}$ decreases rapidly with the increase in chain length (Figure 1).

It should be noted that the $E_{50}$ for a given fatty acid depends upon the concentration of the acid as well as its chain length. This point is demonstrated in Figure 2 where the $E_{50}$ for octanoate

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TABLE I

*The effect of the intraperitoneal injection of the sodium salts of the short chain fatty acids*

| Rat no. | Fatty acid | Conc. *M* | Amount injected *mM/Kg.* | Response | Time until unconscious *minutes* | Duration unconscious *minutes* | $E_{50}$ *mM/Kg.* |
|---|---|---|---|---|---|---|---|
| 1 | Acetate | 1.0 | 20 | None | | | |
| 2 | | | 21 | None | | | |
| 3 | | | 30 | None | | | |
| 4 | | | 33 | None | | | |
| 5 | | | 36 | None | | | |
| 6 | | 2.0 | 56 | Unconsc. | 18 | 15 (died) | |
| 7 | Propionate | 1.0 | 28 | None | | | |
| 8 | | | 28 | None | | | |
| 9 | | | 28 | None | | | |
| 10 | | | 28 | Unconsc. | 18 | 18 | |
| 11 | | | 28 | Unconsc. | 20 | 36 | |
| 12 | | | 30 | None | | | |
| 13 | | | 30 | None | | | 29.0 |
| 14 | | | 30 | Unconsc. | 20 | 4 | |
| 15 | | | 30 | Unconsc. | 20 | 4 | |
| 16 | | | 30 | Unconsc. | 18 | 18 | |
| 17 | Butyrate | 1.0 | 12.5 | None | | | |
| 18 | | | 12.5 | None | | | |
| 19 | | | 12.5 | None | | | |
| 20 | | | 12.5 | None | | | |
| 21 | | | 12.5 | None | | | |
| 22 | | | 14.0 | None | | | |
| 23 | | | 14.0 | None | | | |
| 24 | | | 14.0 | None | | | |
| 25 | | | 14.0 | Unconsc. | 11 | 2 | 14.2 |
| 26 | | | 14.0 | Unconsc. | 11 | 3 | |
| 27 | | | 16.0 | Unconsc. | 14 | 6 | |
| 28 | | | 16.0 | Unconsc. | 8 | 20 | |
| 29 | | | 16.0 | Unconsc. | 8 | 21 | |
| 30 | | | 16.0 | Unconsc. | 7 | 11 | |
| 31 | | | 16.0 | Unconsc. | 7 | 20 | |
| 32 | | | 20.0 | Unconsc. | 11 | 5 | |
| 33 | | | 20.0 | Unconsc. | 9 | 51 | |
| 34 | | | 20.0 | Unconsc. | 8 | 40 | |
| 35 | | | 20.0 | Unconsc. | 7 | 50 | |
| 36 | | | 20.0 | Unconsc. | 6 | 42 | |
| 37 | | 0.5 | 20.0 | None | | | |
| 38 | | | 20.0 | None | | | |
| 39 | | | 20.0 | None | | | |
| 40 | | | 20.0 | None | | | |
| 41 | | | 20.0 | None | | | |
| 42 | | | 23.0 | None | | | |
| 43 | | | 23.0 | None | | | 23.0 |
| 44 | | | 23.0 | Unconsc. | 24 | 2 | |
| 45 | | | 23.0 | Unconsc. | 14 | 12 | |
| 46 | | | 26.0 | Unconsc. | 14 | 1 | |
| 47 | | | 26.0 | Unconsc. | 12 | 5 | |
| 48 | | | 26.0 | Unconsc. | 12 | 7 | |
| 49 | | | 26.0 | Unconsc. | 11 | 9 | |
| 50 | Valerate | 0.67 | 18 | None | | | |
| 51 | | | 18 | None | | | |
| 52 | | | 18 | Unconsc. | 32 | 6 | |
| 53 | | | 18 | Unconsc. | 22 | 28 | |
| 54 | | | 18 | Unconsc. | 22 | 22 | 18.0 |
| 55 | | | 18 | Unconsc. | 22 | 26 | |
| 56 | | | 18 | Unconsc. | 22 | 30 | |
| 57 | | | 18 | Unconsc. | 21 | 44 | |
| 58 | | | 18 | Unconsc. | 20 | 28 | |
| 59 | | 0.50 | 18 | None | | | |
| 60 | | | 18 | None | | | |
| 61 | | | 18 | None | | | |
| 62 | | | 18 | None | | | |

TABLE I—*Continued*

| Rat no. | Fatty acid | Conc. *M* | Amount injected *mM/Kg.* | Response | Time until unconscious *minutes* | Duration unconscious *minutes* | $E_{50}$ *mM/Kg.* |
|---|---|---|---|---|---|---|---|
| 63 | Valerate | | 18 | Unconsc. | 28 | 4 | 19.0 |
| 64 | | | 20 | None | | | |
| 65 | | | 20 | None | | | |
| 66 | | | 20 | Unconsc. | 38 | 10 | |
| 67 | | | 20 | Unconsc. | 18 | 30 | |
| 68 | | | 20 | Unconsc. | 16 | 16 | |
| 69 | | | 22 | Unconsc. | 24 | 8 | |
| 70 | | | 22 | Unconsc. | 16 | 8 | |
| 71 | | | 22 | Unconsc. | 14 | 44 | |
| 72 | | | 22 | Unconsc. | 12 | 32 | |
| 73 | Caproate | 0.50 | 12 | None | | | |
| 74 | | | 12 | None | | | |
| 75 | | | 12 | None | | | |
| 76 | | | 12 | None | | | |
| 77 | | | 12 | Unconsc. | 9 | 2 | 15.0 |
| 78 | | | 14 | None | | | |
| 79 | | | 14 | None | | | |
| 80 | | | 14 | None | | | |
| 81 | | | 14 | None | | | |
| 82 | | | 14 | Unconsc. | 8 | 6 | |
| 83 | | | 15 | None | | | |
| 84 | | | 15 | None | | | |
| 85 | | | 15 | Unconsc. | 9 | 5 | |
| 86 | | | 15 | Unconsc. | 8 | 4 | |
| 87 | | | 15 | Unconsc. | 6 | 6 | |
| 88 | | | 16 | Unconsc. | 9 | 7 | |
| 89 | | | 16 | Unconsc. | 7 | 7 | |
| 90 | | | 16 | Unconsc. | 6 | 10 | |
| 91 | | | 16 | Unconsc. | 5 | 9 | |
| 92 | | | 16 | Unconsc. | 4 | 10 | |
| 93 | Heptanoate | 0.50 | 5 | None | | | |
| 94 | | | 5 | None | | | |
| 95 | | | 5 | None | | | |
| 96 | | | 5 | None | | | |
| 97 | | | 5 | None | | | |
| 98 | | | 6 | None | | | |
| 99 | | | 6 | None | | | |
| 100 | | | 6 | None | | | |
| 101 | | | 6 | Unconsc. | 5 | 5 | 6.2 |
| 102 | | | 6 | Unconsc. | 5 | 6 | |
| 103 | | | 7 | None | | | |
| 104 | | | 7 | Unconsc. | 5 | 5 | |
| 105 | | | 7 | Unconsc. | 5 | 6 | |
| 106 | | | 7 | Unconsc. | 5 | 7 | |
| 107 | | | 7 | Unconsc. | 6 | 7 | |
| 108 | Octanoate | 1.0 | 2 | None | | | |
| 109 | | | 2 | None | | | |
| 110 | | | 2 | Unconsc. | 4 | 4 | |
| 111 | | | 2 | Unconsc. | 3 | 6 | 2.0 |
| 112 | | | 2 | Unconsc. | 2 | 10 | |
| 113 | | 0.5 | 3.4 | None | | | |
| 114 | | | 3.4 | None | | | |
| 115 | | | 3.4 | None | | | |
| 116 | | | 3.4 | None | | | |
| 117 | | | 3.4 | None | | | |
| 118 | | | 3.6 | None | | | |
| 119 | | | 3.6 | None | | | |
| 120 | | | 3.6 | None | | | 3.7 |
| 121 | | | 3.6 | Unconsc. | 5 | 2 | |
| 122 | | | 3.6 | Unconsc. | 5 | 3 | |
| 123 | | | 3.8 | None | | | |
| 124 | | | 3.8 | None | | | |
| 125 | | | 3.8 | Unconsc. | 5 | 3 | |
| 126 | | | 3.8 | Unconsc. | 5 | 5 | |
| 127 | | | 3.8 | Unconsc. | 5 | 5 | |

TABLE I—*Continued*

| Rat no. | Fatty acid | Conc. *M* | Amount injected *mM/Kg.* | Response | Time until unconscious *minutes* | Duration unconscious *minutes* | $E_{50}$ *mM/Kg.* |
|---|---|---|---|---|---|---|---|
| 128 | Octanoate | | 5.0 | Unconsc. | 5 | 7 | |
| 129 | | | 7.5 | Unconsc. | 3 | 32 | |
| 130 | | 0.1 | 6.0 | Unconsc. | 11 | 12 | |
| 131 | | | 6.0 | Unconsc. | 10 | 14 | |
| 132 | | | 6.0 | Unconsc. | 9 | 22 | |
| 133 | | | 6.0 | Unconsc. | 8 | >32 | |
| 134 | | | 6.0 | Unconsc. | 7 | >32 | |
| 135 | Pelargonate | 0.3 | 2.5 | None | | | |
| 136 | | | 2.5 | None | | | |
| 137 | | | 2.5 | None | | | |
| 138 | | | 2.5 | None | | | |
| 139 | | | 2.5 | None | | | |
| 140 | | | 2.7 | None | | | |
| 141 | | | 2.7 | None | | | 2.8 |
| 142 | | | 2.7 | None | | | |
| 143 | | | 2.7 | None | | | |
| 144 | | | 2.7 | Unconsc. | 8 | 2 | |
| 145 | | | 3.0 | Unconsc. | 5 | 4 | |
| 146 | | | 3.0 | Unconsc. | 4 | 8 | |
| 147 | | | 3.0 | Unconsc. | 3 | 6 | |
| 148 | | | 3.0 | Unconsc. | 3 | 10 | |
| 149 | | | 3.0 | Unconsc. | 3 | 10 | |
| 150 | Caprate | 0.1 | 2.8 | None | | | |
| 151 | | | 2.8 | None | | | |
| 152 | | | 2.8 | None | | | |
| 153 | | | 2.8 | None | | | |
| 154 | | | 2.8 | None | | | |
| 155 | | | 3.2 | None | | | |
| 156 | | | 3.2 | None | | | |
| 157 | | | 3.2 | None | | | 3.3 |
| 158 | | | 3.2 | None | | | |
| 159 | | | 3.2 | Unconsc. | 14 | 2 | |
| 160 | | | 3.4 | None | | | |
| 161 | | | 3.4 | None | | | |
| 162 | | | 3.4 | Unconsc. | 7 | 1 | |
| 163 | | | 3.4 | Unconsc. | 4 | 4 | |
| 164 | | | 3.4 | Unconsc. | 4 | 6 | |
| 165 | | | 3.6 | Unconsc. | 7 | 1 | |
| 166 | | | 3.6 | Unconsc. | 5 | 3 | |
| 167 | | | 3.6 | Unconsc. | 5 | 3 | |
| 168 | | | 3.6 | Unconsc. | 5 | 6 | |
| 169 | | | 3.6 | Unconsc. | 7 | 6 | |

as a function of concentration is presented. This pronounced effect of concentration upon the $E_{50}$ is probably a result of a rapid disposal of the fatty acid anion and the influence of concentration upon the rate of absorption from the injection site. With propionate, solutions of low concentration are not effective enough to be adequately studied, whereas with pelargonate and caprate, only solutions of low concentration are sufficiently homogeneous to give reliable results. Therefore, the action of the three, nine and ten carbon members (propionate, pelargonate, and caprate respectively) cannot be quantitatively compared. However, their effectiveness corresponds with the general pattern as seen in Table I.

At the two carbon chain length the narcotic action becomes so weak that large quantities of acetate can be administered without the characteristic effect exhibited by the other acids. The injection of about 56 millimoles per Kg. body weight of 2 M sodium acetate will cause unconsciousness, but the pattern of the response is different. Following the injection of the other fatty acids there is reduced muscular tone and activity, whereas after the injection of the sodium acetate severe muscular spasms and convulsive movements occur. It is interesting to note that the intraperitoneal injection of the same amount (56 millimoles per Kg.) of 2 M NaCl produces the same type of response: that is, a few minutes after the injection the rat

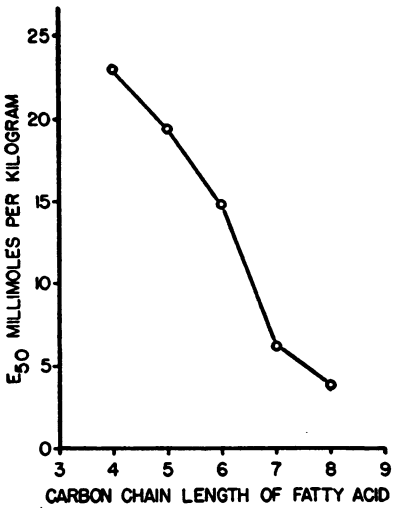


FIG. 1. $E_{50}$ OF FATTY ACID ANION AS A FUNCTION OF CHAIN LENGTH

All acids neutralized to pH 7.4; conc. 0.5 M; given intraperitoneally. Data taken from Table I.

shows muscular twitching which becomes progressively increased until severe muscular spasms cause the animal to thrash about violently. The animal loses consciousness and dies, usually within an hour after the injection. The similarity of the response from the 2 M sodium acetate injection to that from the 2 M NaCl suggests that the mechanism of action here is related to the sodium ion rather than the acetate anion. This effect of high sodium ion has been reported by Ulrich and Shternov (15).

As might be expected, the length of time from injection until unconsciousness, the $E_{50}$, and the length of time of unconsciousness also depend to some extent upon the rate of absorption from the injected site. Consequently, subcutaneous administration is not very effective and nothing more than a sluggishness occurs. Further, the forced feeding of as much as twice the $E_{50}$ will not even produce sluggishness. On the other hand, when the compounds are given intravenously unconsciousness occurs within a few seconds after the injection and with somewhat less than half of the amount necessary to cause unconsciousness with the intraperitoneal route (Table II).

### *Hemolysis*

As it is common knowledge that washed red blood cells will hemolyze when suspended in a sufficiently concentrated solution of the fatty acid anions (16), it seemed reasonable to consider what part hemolysis might play in the reactions which follow fatty acid injection. Accordingly, we have drawn blood by cardiac puncture from rats made unconscious from a fatty acid injection and examined it grossly after centrifugation: in no instance was hemolysis noted.

### *Kidneys*

The fatty acids and some of their metabolic products appear in the urine following their injection (Table III). From these findings we reasoned that the recovery from the narcotic action of the compounds rested mainly in excretion by the kidneys. But this idea was not supported by experiments on nephrectomized rats. The $E_{50}$ and the length of time until recovery in nephrectomized rats seem to be of the same order of magnitude as in the control rats (compare Table IV with Table I).

### *Influence of (OH) group in carbon chain*

To determine if the introduction of a hydroxyl group into the carbon chain would alter the action, we injected lactate and β-hydroxybutyrate and compared their effectiveness with the corresponding fatty acids, propionate and butyrate. The results show that the hydroxy compounds are much less effective (Table V): In fact, the $E_{50}$ for 1 M lactate and β-hydroxybutyrate could not be de-

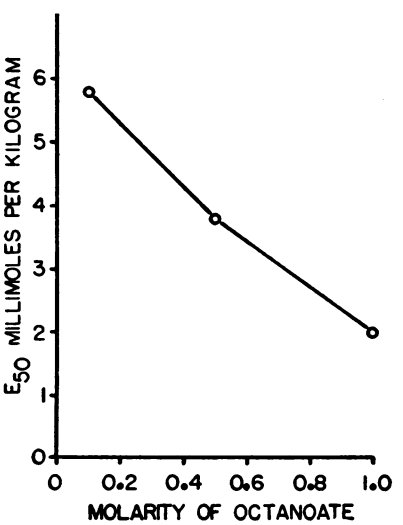


FIG. 2. $E_{50}$ OF SODIUM OCTANOATE AS A FUNCTION OF CONCENTRATION

pH 7.4; given intraperitoneally. Data taken from Table I.

TABLE II

*The effect of the injection site on the response to the sodium salts of the fatty acids*

| Rat no. | Injection site | Fatty acid | Conc. *M* | Amount injected *mM/Kg.* | Response | Time until unconsc. | Duration of unconsc. |
|---|---|---|---|---|---|---|---|
| 170 | Intravenous | Propionate | 1.0 | 12.3 | None | | |
| 171 | (tail vein) | | | 18.0 | Unconsc. | 5 sec. | Died |
| 172 | | | | 19.0 | Unconsc. | 5 sec. | 25 sec. |
| 173 | | Valerate | 1.0 | 2.0 | None | | |
| 174 | | | | 8.8 | None | | |
| 175 | | | | 10.0 | Unconsc. | <1 min. | 2 min. |
| 176 | | | | 12.0 | Unconsc. | <1 min. | 2 min. |
| 177 | | Caproate | 0.5 | 5.6 | None | | |
| 178 | | | | 6.2 | Unconsc. | 30 sec. | 3 min. |
| 179 | | Heptanoate | 0.4 | 1.6 | None | | |
| 180 | | | | 2.0 | Unconsc. | <30 sec. | <30 sec. |
| 181 | | | | 2.0 | Unconsc. | 5 sec. | 55 sec. |
| 182 | | Octanoate | 0.5 | 0.8 | Unconsc. | 5 sec. | 40 sec. |
| 183 | | | | 0.8 | None | | |
| 184 | | | | 1.0 | Unconsc. | 5 sec. | 1 min. |
| 185 | | | | 1.2 | Unconsc. | 20 sec. | 1 min. |
| 186 | | | | 1.5 | Unconsc. | 5 sec. | 3 min. |
| 187 | | Pelargonate | 0.3 | 0.5 | None | | |
| 188 | | | | 0.5 | None | | |
| 189 | | | | 0.7 | Unconsc. | 5 sec. | |
| 190 | | | | 0.7 | Unconsc. | 5 sec. | 160 sec. |
| 191 | | | | 0.7 | Unconsc. | 5 sec. | 6 min. |
| 192 | | Caprate | 0.1 | 0.5 | None | | |
| 193 | | | | 0.6 | Unconsc. | 20 sec. | 1 min. |
| 194 | | | | 0.8 | Unconsc. | 10 sec. | 95 sec. |
| 195 | Subcutaneous | Valerate | 1.0 | 22.0 | None | | |
| 196 | Gastro- | Valerate | 1.0 | 22.0 | None | | |
| 197 | intestinal | | | 22.0 | None | | |
| 198 | (forced | | | 26.0 | None | | |
| 199 | feeding) | | | 35.0 | None | | |

termined because a definitive state of unconsciousness did not occur. Instead, convulsions similar to those seen after the injection of NaCl discussed earlier resulted. With 1 M β-hydroxybutyrate these convulsions occurred after the administration of about 40 millimoles per Kg. body weight, whereas the $E_{50}$ of 1 M butyrate is 14.2 millimoles per Kg. body weight.

TABLE III

*Urine analysis following intraperitoneal injection of the fatty acid salts* *

| Fatty acid injected | Urine analysis | | |
|---|---|---|---|
| | Fatty acid % | Glucose % | Ketones % |
| Propionate (30 *mM/Kg.*) | | 1.0 | 0.05 |
| Butyrate (28 *mM/Kg.*) | 0.2–0.3 | 0.0 | 2.0 |
| Valerate (24 *mM/Kg.*) | 0.4–0.7 | 1.0 | 0.0 |
| Caproate (13 *mM/Kg.*) | 0.2 | 0.0 | 2.0 |
| Octanoate (3.9 *mM/Kg.*) | 0.0 Octanoate 0.1 Butyrate | | |

* Rats fasted 24 hours before experiment. Urine collected for 6 to 12 hours after injection.

### *Alloxan-diabetic rats*

Although the alloxan-diabetic rat does not develop ketosis as is seen in severe human diabetes (17), there is some disturbance of fat metabolism in alloxan diabetes (18) thus it seemed worthwhile to ascertain the susceptibility of alloxan-diabetic rats to the narcotic action of the fatty acid anions. The results of these experiments are given in Table VI. It is clear from these data that the alloxan-diabetic rats were actually less susceptible than normal rats.

### *Mechanism of action*

The narcotic actions studied here are probably a direct action of the fatty acid anion on the cen-

TABLE IV

*The effect of intraperitoneal injection of sodium butyrate and sodium valerate on nephrectomized rats*

| Rat no. | Fatty acid | Conc. *M* | Amount injected *mM/Kg.* | Response | Time until unconsc. *minutes* | Duration of unconsc. *minutes* |
|---|---|---|---|---|---|---|
| 200 | Butyrate | 0.95 | 15.0 | None | | |
| 201 | | | 15.0 | None | | |
| 202 | | | 20.0 | Unconsc. | 11 | 10 |
| 203 | Valerate | 1.0 | 19.5 | None | | |
| 204 | | | | None | | |
| 205 | | | | Unconsc. | 28 | 4 |
| 206 | | | | Unconsc. | 24 | 2 |
| 207 | | | | Unconsc. | 24 | 30 |
| 208 | | | | Unconsc. | 18 | 10 |
| 209 | | | | Unconsc. | 18 | 22 |
| 210 | | | | Unconsc. | 9 | 60 |

tral nervous tissue. The electroencephalographic changes which occur during the unconscious state support this idea (19). The fatty acid salts may inhibit the metabolic activity of cerebral tissue as they do muscle (6) and yeast (1). Several properties characterize their inhibition of yeast cell metabolism: 1. A nonspecificity, as evidenced by the large number of reactions affected, 2. An increasing action with an increase in chain length, 3. A reduction of the inhibitory action when a hydroxyl or carboxyl group is introduced into the hydrocarbon part of the molecules, 4. A reversibility.

The similarity of these properties with those demonstrated in the present study is certainly striking. However, this similarity does not necessarily mean that the cellular mechanism of action is the same in the two situations.

## SUMMARY

Injection of the neutralized short chain fatty acids will produce unconsciousness in experimental animals. The amount of the fatty acid which will produce this response decreases with an increase in chain length. Further, the amount which will produce a loss of consciousness for a given fatty acid depends upon the concentration and the site of injection. The introduction of an (OH) group into the carbon chain reduces the narcotic action.

TABLE V

*The effect of intraperitoneal injection of sodium lactate, sodium β-hydroxybutyrate and acetone on rats*

| Rat no. | Compound injected | Conc. *M* | Amount injected *mM/Kg.* | Reaction |
|---|---|---|---|---|
| 211 | Sodium | 0.5 | 30 | Sluggish movements, no loss of consciousness |
| 212 | lactate | 1.0 | 30 | Sluggish movements, no loss of consciousness |
| 213 | | | 30 | Sluggish movements, no loss of consciousness |
| 214 | | | 34 | Sluggish movements, no loss of consciousness |
| 215 | | | 34 | Sluggish movements, no loss of consciousness |
| 216 | | | 36 | Sluggish movements, no loss of consciousness |
| 217 | | | 38 | Sluggish movements, no loss of consciousness |
| 218 | | | 38 | Sluggish movements, no loss of consciousness |
| 219 | Sodium | 0.5 | 30 | No loss of consciousness |
| 220 | β-hydroxy | 1.0 | 30 | No loss of consciousness |
| 221 | butyrate | | 40 | Severe muscular spasms and death in 57 min.; righting reflexes present until death. |
| 222 | | | 50 | Severe muscular spasms; righting reflexes present until death in about one hour. |
| 223 | Acetone | 1.0 | 7 | No loss of consciousness |
| 224 | | | 37 | No loss of consciousness |
| 225 | | | 40 | No loss of consciousness |
| 226 | | | 50 | No loss of consciousness |
| 227 | | | 60 | No loss of consciousness |
| 228 | | | 80 | Loss of consciousness for five minutes, approximately four minutes after injection. |

TABLE VI

*The effect of intraperitoneal injection of sodium valerate on alloxan-diabetic rats*

| Rat no. | Fatty acid | Conc. *M* | Amount injected *mM/Kg.* | Response | Time until unconsc. *minutes* | Duration of unconsc. *minutes* |
|---|---|---|---|---|---|---|
| 229 | Valerate | 0.5 | 18 | None | | |
| 230 | | | | None | | |
| 231 | | | | None | | |
| 232 | | | | None | | |
| 233 | | | 20 | None | | |
| 234 | | | | None | | |
| 235 | | | | None | | |
| 236 | | | | Unconsc. | 20 | 6 |
| 237 | | | 22 | None | | |
| 238 | | | | None | | |
| 239 | | | | Unconsc. | 28 | 4 |
| 240 | | | | Unconsc. | 16 | 20 |
| 241 | | | 24 | Unconsc. | 38 | 2 |
| 242 | | | | Unconsc. | 22 | 6 |
| 243 | | | | Unconsc. | 16 | 12 |

There is no hemolysis from the amount of fatty acid which will produce unconsciousness. Nephrectomy does not seem to alter the duration of the narcotic action.

It is suggested that the mechanism of action at the cellular level may be the same as that in the fatty acid inhibition of yeast metabolism.

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