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Effect of Cesium and Ethanol on Tumor Bearing Rats

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MESSIHA, F S *Effect of cesium and ethanol on tumor bearing rats* PHARMACOL BIOCHEM BEHAV 21: Suppl 1, 35–40, 1984 —The effect of separate and combined administration of 15% ethanol and 0 2% CsCl solution on life span of rats with Novikoff hepatoma implants was studied as a function of time of initiation of treatment Pretreatment with CsCl alone or combined with ethanol resulted in earlier onset on morbidity compared to the ethanol-treatment or to controls As high as 87 5% of Cs-treated animals died 16 days post tumor implantation compared to 33% of rats receiving CsCl and ethanol combined This protective action of ethanol against Cs-evoked toxicity in tumor-bearing rats persisted through the experiment Animals subjected to drug treatment immediately after tumor transplantation displayed delayed onset of morbidity compared to drug pretreated rats. In both cases the Cs-treatment enhanced morbidity by approximately 2 folds from corresponding controls. Animals sacrificed 18 days post tumor inoculation showed an induction of hepatic alcohol dehydrogenase and an increase in V_{max} without changes in the apparent K_m by the Cs-treatment There was an increase in liver mitochondrial aldehyde dehydrogenase of hepatoma-bearing rats from tumor-free controls which was associated with an increase in the apparent K_m value. The results indicate potentiation of the hepatoma toxicity by CsCl which may be minimized by ethanol. A role for hepatic enzymes determined in the pathogenesis of tumor line studied and/or their use as a biochemical correlate is suggested

Alcohol dehydrogenase Aldehyde dehydrogenase Cesium chloride Ethanol Hepatoma Morbidity

EXPERIMENTAL evidence from this laboratory suggests a paradoxical relationship between cesium (Cs) salts and ethanol (ET). This has been shown by Cs-produced aversion to voluntary intake of ET by the rat [10,12] and to Cs-mediated decrease in the duration of ET narcosis in mice [11]. The observations that CsCl may possess antitumor activity in rodents [3, 7, 13, 15, 19, 23, 29], in man [25] and the increased incidence of certain head, neck, liver, lung and rectal cancers among alcoholics [9, 20, 21, 24, 28, 30] have provided the rational of the present study to evaluate the effect of CsCl and ET alone and combined on tumor-bearing rats. Moreover, an interaction between Cs^+ and ET seems likely due to ET-produced membrane fluidity [6] and to Cs^+ evoked intercellular electrolyte changes, i.e., by substituting for K^+ [22], which may then alter the transmembrane potential implicated in tumorgenesis [4,5].

This study assesses the effect of separate and combined administration of ET and CsCl on rats bearing a tumor line which often displays an enlargement of the liver and produces enhanced mitotic activity, i.e., Navikoff's hepatoma (NH). In addition, measurements of the hepatic enzymes primarily involved in ET and in acetaldehyde detoxifications were made due to the implication of liver aldehyde dehydrogenase (L-ALDH) in certain hepatocarcinogenesis.

METHOD

The subjects were Sprague Dawley female rats aged 31 to 34 days at the beginning of the experiments They were housed in groups of 3 and were maintained on purina pellet food and water ad lib for a 3 day acclimatization period prior to initiation of the experiments. In the first set of experiments, the effect of CsCl and ET on life span of NH-bearing rats was studied. Animals were divided into 4 groups of 24 rats each. They had access to distilled water (controls), 15% (w/v) ET, 0.2% CsCl or both combined in identical concentration as the sole drinking fluid for 12 consecutive days prior to interperitoneal (IP) injection of 1.0 ml of viable cell suspension of NH [18]. Additional four groups of 6 rats each served as drug-controls by receiving identical drug concentration in their drinking fluid ad lib but remained tumor free. Animals continued to receive their assigned drinking fluids for a 4-week period post inoculation with exception of the CsCl solution which was increased to 0.4% concentration. Body weight and fluid consumptions were monitored daily. Amounts of Cs intake were expressed as mEq/kg/24 hr and both ET and water consumption were given as mg/kg/24 hr. Mortality score was recorded in cumulative fashion and expressed as percent death occurring from the initial number used for each treatment group.

In the second set of experiments, the effect of ET and CsCl alone and combined on the life span of NH-bearing rats was tested immediately after inoculation with NH. Thirty-two female rats were maintained on distilled water ad lib for 12 days They were then divided into 4 subgroups of 8 animals each and were inoculated IP with 1.0 ml NH cell suspension and then received either distilled water, 15% ET, 0.4% CsCl or both of ET and 0.4% CsCl combined through-

TABLE 1

EFFECT OF SEPARATE AND COMBINED CESIUM CHLORIDE AND ETHANOL ON THE RAT BODY WEIGHT PRIOR TO AND AFTER INOCULATION WITH NOVIKOFF'S HEPATOMA

Treatment	Inoculation	Days of Drug Pretreatment			Days Post Inoculation	
		Initial	7	12	7	15
Controls	None	105 4 ± 2 5	143 8 ± 6 1	180 4 ± 6 5	213 0 ± 3 0	235 1 ± 5 1
	Inoculation	106 1 ± 2 6	155 7 ± 3 1	168 6 ± 5 4	207 5 ± 4 3	228 2 ± 6 5
Ethanol	None	111 1 ± 3 8	117 0 ± 4 5	141 7 ± 5 7	158.6 ± 5 0	193 6 ± 2 4
	Inoculation	108 5 ± 2 9	124 4 ± 3 8	148 2 ± 3 9	188 5 ± 4 0	200 8 ± 7 8
CsCl	None	111 5 ± 3 4	148 7 ± 3 7	173 6 ± 4 6	117 1 ± 22 9	122 2 ± 15 9
	Inoculation	109 3 ± 3 3	153 3 ± 3 5	144 7 ± 4 8	151 0 ± 6 5	No Survivals
Ethanol + CsCl	None	108 4 ± 4 0	109 5 ± 5 1	116 0 ± 7 4	168 0 ± 9 3	162 6 ± 10 1
	Inoculation	107 6 ± 3 4	116 2 ± 5 0	134 3 ± 3 9	136 2 ± 8 5	129 8 ± 9 7

Animals were 34 days old initially and received the drugs dissolved in distilled water ad lib The CsCl solution was 0 2% and 0 4% for the pre- and post-inoculation period, respectively The ethanol solution remained at 15% (w/v) throughout the study Values are means ± SE of mean bodyweight of the initial 24 rats for each treatment group Number of animals varied during post inoculation period due to death occurrance

out a subsequent 32 day observation period. Mortality score was recorded as mentioned above.

In the third set of experiments, the effect of short-term intake of 15% ET, 0.2% CsCl alone and combined on rat liver alcohol dehydrogenase (L-ADH) and L-ALDH was studied as a function of pair feeding and of NH inoculation. Twenty-four female rats were divided into 4 groups of 6 animals each who received either distilled water, 15% ET, 0.2% CsCl or both combined as the sole drinking fluid for 12 consecutive days prior to their sacrifice for the enzymatic determinations The animals were pair-fed against the water controls In addition, 48 female rats of comparable age were divided into four groups of 12 animals each which were similarly treated for 12 consecutive days with identical drug levels made available in their drinking fluid. Thereafter, 6 rats of each group were inoculated with 1 0 ml of NH cell suspension and the remainder were injected saline and remained tumor-free throughout the experiment. The drug regimens were continued for a subsequent 18 days before the animals were sacrificed Animals were killed by decapitation and the livers were quickly removed, weighed and individually homogenized in KCl buffer prior to the subcellular fractionation [14] of the mitochondrial (MT) and the cytoplasmic (CT) fractions which were used as the source for the L-ADH [2] and the L-ALDH [1] determinations. Protein measurements were made according to the biuret assay and the enzymatic activity was expressed as specific activity, nMol/min/mg protein, measured at 30°C The Lineweaver and Burk method [8] was utilized for the estimation of the maximal velocity of the reaction (V_{max}) and the Michales-Menten constant (K_m).

RESULTS

Table 1 lists changes in body weight of female rats treated with either CsCl or ET alone or both combined as a function of inoculation with viable cell suspension of NH There was an increase in body weight of water controls in the range between 60 g and 75 g compared to 30 g to 40 g weight gain of ET-treated rats ($p<0.02$) for the initial 12 days preceding NH implantation. Little change in body weight occurred by the Cs-treatment for the same period Conversely, rats receiving ET and CsCl concomitantly showed as little as 8 g to 25 g gain in body weight for the initial 12 day period ($p<0$ 02) No change was noted in the body weight of animals maintained on water or on ET for 15 days subsequent tumor inoculation compared to corresponding tumor-free controls This is contrasted with a massive loss in weight gain of Cs-treated rats after tumor implantation which was also evident by the concurrent administration of ET with CsCl.

Figure 1 illustrates the amounts of Cs^+, mEq/kg/24 hr, and ET intake, mg/kg/14 hr, consumed when were administered alone or combined. The upper panel of Fig 1 shows low Cs^+ consumption when CsCl was coadministered with ET than when it was given in water for the 12 days before and shortly after inoculation with NH until the death of the Cs-treated animals. A decrease in water intake occurred subsequent tumor transplantation from the preceding tumor-free period The lower panel of Fig. 1 demonstrates the animal's self-titration of daily ET consumption when administered alone or combined with CsCl which tended to increase in animals receiving drug combination

Figure 2 illustrates mortality score produced by NH of rats treated with 15% ET or CsCl alone or combined for 12 days prior to (upper panel) or immediately after tumor transplantation (lower panel) A shift in mortality curve to the left was noted in rats treated with Cs alone or combined with ET from water controls. This is demonstrated by a 12 5% initial death of Cs-treated rats occurring only 3 days post inoculation compared to 4% recorded for the water controls and the ET drinking rats 5 days later. The upper panel of Fig. 1 also shows that 87 5% of Cs-pretreated animals were dead 16 days post tumor transplantation compared to 67% of Cs plus ET consuming animals and 33% of the controls This ET-mediated prolongation of life expectancy in the presence of Cs was evident at the end of the 24 day observation period as shown by a similar morbidity score of 42% for water control and ET drinking rats compared to 88% and

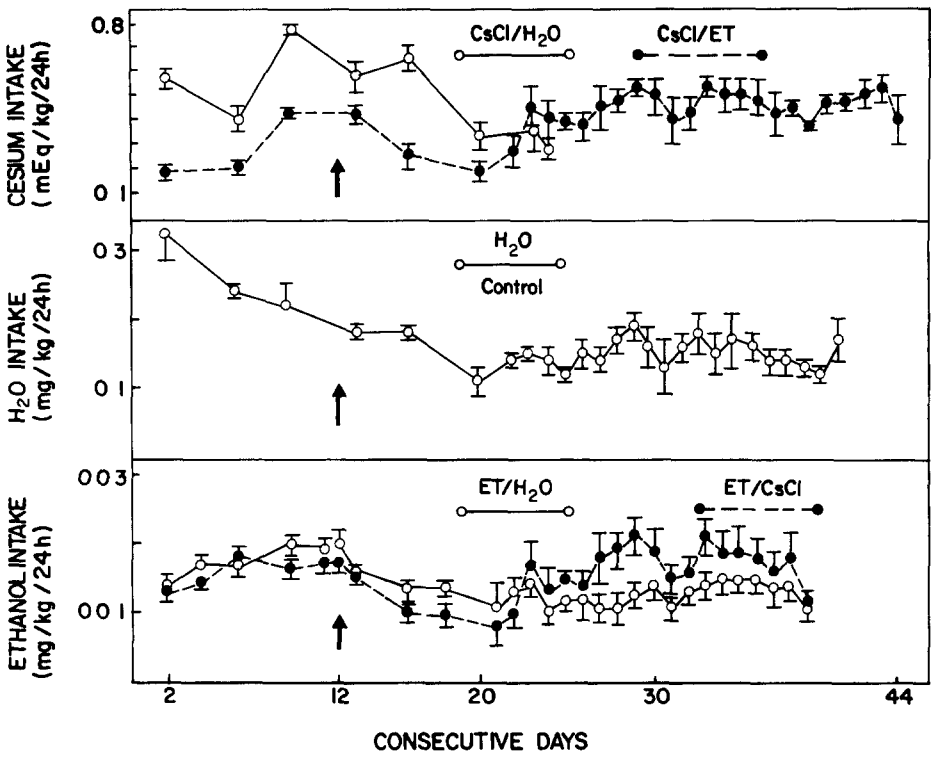

FIG. 1 Daily drug consumption prior to and post inoculation with Novikoff hepatoma by female rats as a function of time. Rats, 24 animals per group, received either distilled water (H_2O—control), 0.2% CsCl solution ($CsCl/H_2O$), 15% ethanol (ET/H_2O) or same concentration of CsCl dissolved in 15% ethanol (CsCl/ET) as the only drinking fluid ad lib. Drug concentration was expressed as mg/kg/24 hr and mEq/kg/24 hr for ET and Cs^+, respectively. Water consumption was also expressed as mg/kg/24 hr. The arrows indicate time of tumor transplantation. The Cs-treated rats ($CsCl/H_2O$) reached maximal mortality at the time shown in the upper panel and no adequate number of survivals was available for determination of the mean ±SE of the mean.

75% death in Cs and Cs plus ET treated rats, respectively. This shift in morbidity score by the Cs treatment was not evident when drug treatment began immediately after tumor inoculation (Fig. 2, lower panel). The use of a 0.4% CsCl as the drinking fluid resulted in 100% death of animals 20 days post inoculation with NH while a 50% morbidity occurred when identical CsCl concentration was coadministered with 15% ET which was similar to that determined for the ET and water drinking rats.

Table 2 lists specific activities of hepatic ADH and ALDH of rats receiving identical CsCl and ET treatment to those used preceding inoculation with NH. Specific activities of L-ADH and L-ALDH did not differ among treatment groups studied when they were pair-fed. Intake of CsCl dissolved in water or in 15% ET solution by rats not pair-fed moderately decreased L-ADH. However, this L-ADH inhibition was not statistically significant from water controls. This decrease of L-ADH was more apparent when compared to pair-fed rats treated with CsCl alone ($p<0.02$) or with ET combined ($p<0.01$).

Table 3 summarizes the effect of NH on specific activities of L-ADH and L-ALDH and their kinetics as a function of the Cs-treatment. The NH-bearing rats showed a 61% induction of endogenous L-ADH by the Cs-treatment from corresponding controls. This was associated with a marked rise in V_{max} without a concomitant change in the apparent K_m. Hepatic CT and MT-ALDH were not altered by CsCl with exception of an increase in K_m of L-MT-ALDH of NH-bearing rats from non-inoculated controls.

DISCUSSION

Animals treated with 0.2% CsCl or 15% ET for 12 consecutive days showed little or marked decrease in weight gain from water controls, respectively. However, this ET-mediated adverse reaction was not manifested in mortality score in NH-bearing rats since both the ET treatment and water controls scored identical on both initial and final mortality scores. This is contrasted with a marked reduction in animals growth by the CsCl and ET combination for the same 12 day period. This can not account for the amounts of Cs^+ intake since the rats consumed less Cs^+ when coadministered with ET than when it was given alone for the initial 12 days. It seems likely that the addition of CsCl to ET drinking regimen potentiated the ET-effect on body weight in general, i.e., by interferring in carbohydrate metabolism, and enhancement of ET "negative" calories by Cs^+. However, prolonged treatment with CsCl reduced body weight more than the ET treatment. For example, a 48% and 18% decrease in body weight was noted by Cs and ET in non-

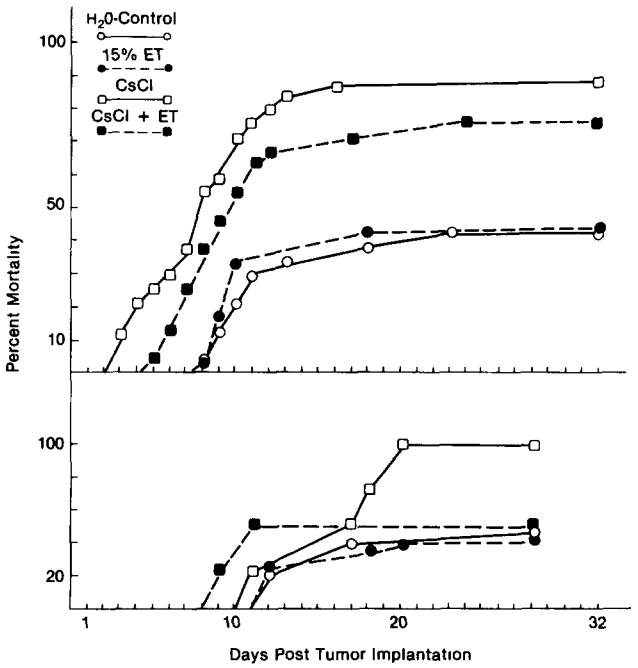

FIG 2 Effect of separate and combined administration of CsCl and 15% ethanol on life span of Novikoff's hepatoma bearing rats The upper panel shows morbidity score of rats receiving drug treatment for 12 consecutive days prior to tumor transplantation which was continued for a subsequent 32 day observation period Four groups of animals each consisting of 24 female rats received either 0 2% CsCl dissolved in water, 15% (w/v) ethanol (ET) solution or same concentration of CsCl dissolved in the 15% ethanol (CsCl + ET) or distilled water (H_2O-controls) as the sole drinking fluid The lower panel shows cumulative morbidity score as a function of time in female rats receiving identical treatment as above, with exception of the use of a 0.4% CsCl solution, which began immediately after Novikoff's hepatoma transplantation The morbidity score is expressed as percent death of animals from initial number used

inoculated animals, respectively This may be due to tissue accumulation of Cs^+ as a function of prolonged treatment and/or may be related to the route of CsCl administration since IP injection of larger daily dosage of CsCl, 1.0 mEq/kg, for as long as 40 days did not adversely affect body weight [27]. This is compared to the present results obtained with a smaller daily intake of Cs^+ between 0 5 and 0 6 mEq/kg for a 27 day period post inoculation with NH.

A vehicle-dependent drug consumption was noted before and after tumor implantation For example, during preinoculation period a reduction in Cs^+ consumption occurred when it was dissolved in ET than in water This is compared to equal consumption of ET in the presence and in the absence of CsCl initially which tended to increase for the post-tumor transplantation period for the ET solution contained CsCl This may account to Cs^+ antagonism to some of ET-evoked responses [10–12, 16] resulting in more ET consumption to perceive same ET evoked responses

The mortality score of the present study shows that Cs-treatment markedly enhanced NH toxicity as demonstrated by earlier death of animals pretreated with 0 2% CsCl regardless of the vehicle being used. Moreover, animals receiving the higher 0 4% CsCl solution subsequent to the NH-transplantation showed a delay in onset time of death from rats pretreated with 0 2% CsCl before inoculation with same tumor This also strongly suggests of Cs-mediated toxicity in conjunction with NH which is consistent with the observed reduction of the life span of NH-bearing rats from corresponding control by CsCl These results suggest that Cs^+ was not only an ineffective agent in the tumor studied, but also exerted additive toxicity Accordingly, the need for more investigations related to antitumor efficacy of Cs-salts and to Cs-tumor toxic interaction is indicated

In this study, ET consumption did not alter mortality of NH-bearing rats from controls However, it appears that ET may have exerted some protective action against the Cs toxicity when coadministered with CsCl immediately after inoculation This may account to ET-interference in Cs absorbtion and/or to Cs-produced enhancement of ET penetra-

TABLE 2

EFFECT OF SEPARATE AND COMBINED SHORT-TERM ADMINISTRATION OF ETHANOL AND CSCl ON SPECIFIC ACTIVITIES OF ENDOGENOUS HEPATIC ALCOHOL DEHYDROGENASE (L-ADH) AND ALDEHYDE DEHYDROGENASE (L-ALDH) AS A FUNCTION OF PAIR FEEDING

	Pair-Fed		Non Pair Fed		
Treatment	L-ADH	L-CT-ALDH	L-ADH	L-CT-ADLH	L-MT-ALDH
Controls	11 0 ± 1 5	18 4 ± 0 5	10 6 ± 0 7	16 7 ± 0 9	17 1 ± 0 8
15% Ethanol	10 3 ± 0 8	18 1 ± 1 4	10 2 ± 0 8	16 5 ± 1 3	16 5 ± 1 8
0 2% CsCl	13 6 ± 0 6	21 0 ± 1 6	9 0 ± 0 7	16 1 ± 1 4	18 9 ± 1 6
15% Ethanol + 0 2% CsCl	12 9 ± 1 0	21 1 ± 0 6	8 4 ± 0 6	16 4 ± 1 6	17 8 ± 1 9

Each value represents the mean of 6 independent determinations ± SE of the mean of specific activity of (nMol/min/mg protein) of hepatic ADH and ALDH in mitochondrial (MT) and cytoplasmic (CT) fractions Drinking fluid consisted of either distilled water, 0 2% CsCl, 15% ethanol or both 15% ethanol and CsCl combined ad lib for 12 consecutive days

TABLE 3

KINETIC DATA FOR LIVER ALCOHOL DEHYDROGENASE (L-ADH) AND ALDEHYDE DEHYDROGENASE (L-ALDH) AS A FUNCTION OF ADMINISTRATION OF 0 2% SOLUTION OF NOVIKOFF HEPATOMA (NH) BEARING RATS

	L-ADH			L-CT-ALDH			L-MT-ALDH		
Treatment	Spec. Activ	V_{max}	K_m	Spec. Activ	V_{max}	K_m	Spec Activ.	V_{max}	K_m
Controls (non-inoculated)	17 3 ± 1 4	17 4	0 07	22 2 ± 1 7	22 6	0 33	34 7 ± 1 9	58.9	6.04
Controls (inoculated with NH)	13.7 ± 1 2	15 1	0 11	25 3 ± 1 9	24 9	0 51	35 5 ± 2.3	70 0	8 32
CsCl (inoculated with NH)	22 1 ± 1 0*	25 0	0 09	23 9 ± 2 3	25 0	0 40	35 0 ± 2 8	65 0	9 26

Animals had access to distilled water (control), 0 2% CsCl as the only drinking fluid available for 12 and 18 days pre- and post-inoculation with viable Novikoff hepatoma cell suspension, respectively Specific activity (Spec Act) derived from 5 independent determinations. The kinetics were determined by the Lineweaver and Burk method and represent the mean of 3 estimation for V_{max} and K_m values (mMol)
*$p<0$ 05

tion into tissue which may produce certain protective action as reported for certain types of cancers [17,26]. Conversely, ET may have facilitated Cs-penetration into the tumor tissue resulting in changes of pH required for tumor progression and development

The enzymatic part of this study shows that separate or combined administration of CsCl and ET for 12 days produced little changes in endogenous hepatic ADH and ALDH in both pair-fed and of non pair-fed rats. However, the latter group showed a decrease in specific activity of L-ADH in animals receiving CsCl alone or combined with ET compared to corresponding pair-fed rats. This may reflect a hepatotoxicity of Cs^+ under the experimental conditions used Moreover, the kinetics of this study also indicate the susceptibility of L-ADH to hepatoma cell line used as demonstrated by a reduction of L-ADH in NH-bearing rats compared to controls. However, the Cs-treatment of NH-bearing rats was associated with induction of L-ADH from controls and of an increase in V_{max} but without a concomitant change in the apparent K_m. This may be related to Cs-mediated increase in protein synthesis without altering the K_m property of the enzyme.

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