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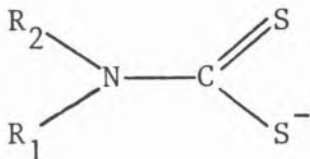
MARK M. JONES
SHIRLEY G. JONES
WILLIAM M. MITCHELL
Departments of Chemistry and Pathology
and
Center in Molecular Toxicology
Vanderbilt University
Nashville, Tennessee 37235
U.S.A.

STRUCTURE-ACTIVITY RELATIONSHIPS IN THERAPEUTIC CHELATING AGENTS

The examination of the action of a number of structurally related dithiocarbamates as antagonists for acute and chronic cadmium intoxication reveals a number of relationships involving structural parameters and various measures of antagonist efficacy. The structural features also have a pronounced effect on the histopathology of the liver and kidney in treated animals.

The report by GALE *et al.* [1] of the ability of sodium diethyldithiocarbamate to antagonize the acute toxicity of cadmium chloride led us to examine this action in some detail [2-6]. We found that while sodium diethyldithiocarbamate was, in fact, an effective antagonist, its use led to increased levels of cadmium in the brain. Subsequently, preparation and testing of a large number of structurally related dithiocarbamates led to the discovery that alterations in the brain levels of cadmium were strongly dependent on the groups attached to the dithiocarbamate moiety and that the transport of cadmium into the brain could be reduced by the use of substituents with more polar components.

All of the compounds examined had the chelating group



present, with R_1 and R_2 varied. The differences in the relative polarities of compounds in this series were estimated as roughly equivalent to the differences in the sums of the π constants for the groups R_1 and R_2 . Each compound was thus characterized by the term $(\pi_1 + \pi_2)$ where π_1 is the π constant of HANSCH and LEO [7] for R_1 and π_2 that for R_2 . It was found that compounds with strongly polar (or ionic groups) as well as those with very non-polar substituents were both less effective as antagonists than compounds whose R groups were of intermediate polarity (*i.e.* those bearing $-OH$ groups). The measures of activity used include the following: survival ratios in acute cadmium chloride intoxication and relative cadmium levels in various organs (brain, liver or kidney) as well as composite measures which had two or more of these factors given various relative weights.

The pathological changes (in animals with chronic cadmium intoxication) subsequent to the use of these chelating agents to mobilize the cadmium are also very strongly dependent upon the structure of the chelating agent utilized to effect the mobilization.

Because the organ distribution of various toxic metals is not identical, different relationships between structure and activity of chelating agents can be anticipated, and indeed are found [8,9] for other toxic metallic species.

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SONIA APELGOT

ALAIN JOSEPH

JACQUES COPPEY

Institut Curie

11, rue Pierre et Marie Curie 75231

Paris Cédex 05

France

ALAIN GAUDEMER

ISABELLE SASAKI

DANIÈLE PRASEUTH

Laboratoire de Chimie de Coordination Bioorganique

LA 255, Université Paris-Sud

91405 — Orsay

France

ETIENNE GUILLE

JANINE GRISVARD

IGOR SISOËFF

Laboratoire de Biologie Moléculaire Végétale

LA 40, Université Paris-Sud

91405 — Orsay

France

LETHAL EFFECT OF EITHER $^{64}\text{CuCl}_2$ OR $^{64}\text{Cu-TMPyP}$ INCORPORATED IN HUMAN MALIGNANT CELLS

This study was performed with A549 human malignant cells. The cells were in contact with the radioactive compound for 14, 24 or 43 hours, then washed and numerated. The incorporated radioactivity was determined as well as the Cloning

Forming Capability (C.F.C) of the cells. A clear lethal effect was observed. When the survival is expressed as a function of the radioactivity present in the growth medium (uCi/ml) at the beginning of the contact period, exponential curves were obtained either for $^{64}\text{CuCl}_2$ or for $^{64}\text{Cu-TMPyP}$ (TMPyP = Tetra methyl pyridine porphine). The slope of the curve obtained when $^{64}\text{Cu-TMPyP}$ was used is 1.5 time greater than that with $^{64}\text{CuCl}_2$.

This study and control experiments show that:

- 1) The lethal effect observed is not a consequence of the irradiation by the particules emitted by ^{64}Cu but a consequence of the decay itself.
 - 2) Each survival curve is characterized as a single exponential curve although the cells are in non-synchronized growth conditions. This result implies that the incorporation of ^{64}Cu in the compartment implicated in the lethal effect is independent of DNA synthesis.
 - 3) All experiments performed to study the lethal effect of intracellular decay of radioactive isotopes have shown that an exponential survival curve is always related to decays occurring inside the DNA molecule only.
 - 4) We detected ^{64}Cu bound to DNA whatever $^{64}\text{CuCl}_2$ or $^{64}\text{Cu-TMPyP}$ was used. Experiments are still in progress in order to evaluate the number of ^{64}Cu atoms bound to the DNA molecule and to evidence a relationship with the different lethal efficiency of this two compounds.
- A lethal effect of ^{65}Zn via decay has been also observed for A549 cells labelled with $^{65}\text{ZnCl}_2$.