Una nuova classe di composti ad azione antiulcera: gli esteri farnesilacetici

Il primo accenno ad un fattore alimentare necessario per il mantenimento dell'integrità anatomica della mucosa gastrica risale al 1929 ed è dovuto a DAM[1,2] che postulò l'esistenza di un fattore antiulcera nel corso delle ricerche che dovevano portarlo alla scoperta della vitamina K.

I tentativi di isolare questa cosiddetta Vitamina U (U-factor, Antiulcusfaktor) dal cavolo cappuccio e da altri vegetali non hanno finora avuto, per quanto mi consta, alcun successo.

L'attribuzione di attività antiulcera al metionin-metilsolfonio presente nel cavolo cappuccio[3] si è dimostrata infondata[4]; lo stesso può dirsi per la *L*(+)-glutammina[5].

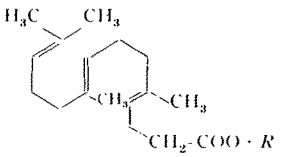
Anche nel nostro laboratorio i tentativi di isolamento della vitamina U sono stati infruttuosi tanto da indurmi a battere un'altra strada, che pur deviando dal campo delle sostanze naturali ha consentito di riconoscere l'esistenza di una nuova classe di composti sintetici dotati di elevata attività antiulcera.

Dalla letteratura sembra risultare che il fattore U è liposolubile[6]; d'altro lato era stato messo in evidenza che nei polli, in seguito a diete carenzate, si formano erosioni nel ventriglio: il fattore la di cui carenza è responsabile di questa forma morbosa («antigizzard-erosion factor») è liposolubile, è in rapporto con la vitamina K ed è presente, tra l'altro, nel cavolo[7,8]. Nel cavolo è anche presente la vitamina K_1.

Mi sono perciò chiesto se l'attività antiulcera potesse dipendere da composti del tipo di quelli delle catene laterali terpeniche delle vitamine K naturali, ed ho sperimentato il farnesolo e il fitolo, usando come test l'ulcera da istamina nella cavia protetta con tripelennamina, test molto sensibile e da noi largamente studiato ed usato per l'accertamento dell'attività U degli estratti di cavolo[9,10].

La scelta del farnesolo come punto di partenza di queste ricerche è stata particolarmente fortunata, perchè a differenza del fitolo, che è risultato inattivo, questo alcool terpenico ha dimostrato una buona attività antiulcera, non solo per via orale, ma anche parenterale, a dosi relativamente basse (10 mg/kg).

Proseguendo le ricerche su terpeni naturali analoghi, si mise in evidenza l'importanza della struttura isoprenica per l'azione antiulcera. Vennero allora preparati diversi composti sintetici a partire dal farnesolo, tra cui l'acido farnesilacetico, che si dimostrò pure attivo. La massima attività fu però riscontrata negli esteri di questo acido, e in particolare nei farnesilacetati di etile, butile, laurile, allile, propargile, cicloesile, fitile, geranile, tetraidrogeranile e farnesile, che si dimostrarono attivi a dosi inferiori a 5 mg/kg.



Questi nuovi composti[11] sono particolarmente interessanti per la tossicità praticamente trascurabile unita ad un'elevata attività antiulcera, che non è in rapporto con veruna azione neurovegetativa; non sono infatti anticolinergici, nè gangliopleglci, nè antistaminici, nè spasmolitici, e neppure modificano la secrezione gastrica. Il loro meccanismo di azione, peraltro non chiarito, sembra consistere in un effetto protettivo e rigenerativo di determinate mucose. Estese ricerche farmacologiche sui termini più interessanti della serie hanno messo in evidenza che l'azione antiulcera è, se non l'unica, certamente di gran lunga la più importante tra le poche osservate, sì da far pensare ad una vera e propria specificità in questo campo.

Preliminari esperienze cliniche nell'ulcera gastrica e nell'ulcera duodenale confermano i risultati della sperimentazione sull'animale.

Summary. In a new series of synthetic compounds, the farnesyl acetic esters, some specifically effective drugs for the treatment of experimental gastric ulcer have been singled out. They have shown to be completely lacking of neurovegetative actions.

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Absence of Phosphogluconate Pathway Activity in Normal and in Ethanol-Intoxicated Slices from Rat Brain

The question of whether the brain possesses a functional phosphogluconate or 'direct oxidative' pathway has not been resolved. Although the glucose-6-phosphate and 6-phosphogluconate dehydrogenases can be demonstrated in brain[1], the role of this pathway has been considered negligible[2]. Ethanol has been shown to influence the γ-aminobutyric acid content of rat brain[3] and since the metabolism of the latter compound serves as a by-pass of the α-ketoglutarate-succinate transformation in the citric acid cycle, it was decided to investigate the influence of ethanol on the pathway of glucose oxidation in this tissue.

Slices of cerebral cortex (350 mg) from 200–250 g Sprague-Dawley albino rats were incubated in special flasks[4] with 20 mg glucose containing 0.2 μC of either glucose-1-C^{14} or glucose-6-C^{14} in 5 ml of Krebs-Ringer bicarbonate solution in which the KCl concentration was increased to 0.1 molar[5]. This approximates the K^+ con-

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centration of nerve cells *in vivo* and about doubles the normal respiration of brain slices in the presence of glucose. Other incubation flasks contained, in addition, 12.5 mg ethanol, 25 μg acetaldehyde, and 250 μg acetate which correspond to levels of these substances present in blood after an acute dose of ethanol. Flasks were swept with 95% O_2–5% CO_2 before closing and incubated with shaking at 37°C for 90 min. Then 0.5 ml 30% KOH was injected into the center well which contained a small role of filter paper, and 0.2 ml 10*N* H_2SO_4 was tipped into the main body of the flask from the side arm. After shaking the flask and its contents for an additional hour the filter paper and contents of the center well were quantitatively removed and diluted to 10 ml. The capped tubes were allowed to stand for 16 h with occasional shaking at room temperature to assure complete elution of carbonate from the paper. Aliquots were precipitated with $BaCl_2$ containing NH_4Cl in the presence of carrier K_2CO_3 and 'infinitely thick' layers of $BaC^{14}O_3$ were mounted and assayed for radioactivity in a micromil window-equipped flow counter. Sufficient counts were totaled so that the counting error was less than 4% at the 0.05 level of significance. The activity of the glucose-1-C^{14} and glucose-6-C^{14} used in these experiments was determined after complete oxidation to $C^{14}O_2$ by potassium persulfate[6].

Incubations of only 90 min were used in order to minimize any effects due to recycling and randomization of the carbon atoms of glucose, since it has been shown that in mammary tissue the ratio of $C^{14}O_2$ from glucose-1-C^{14} to $C^{14}O_2$ from glucose-6-C^{14} is much higher after 1 h incubation than after 2 and 3 h periods[7]. This precaution, plus the use of K^+ stimulated brain slices, produced more valid experimental conditions than those existing in earlier investigations.

The Table shows that the ratio of $C^{14}O_2$ from the oxidation of glucose-1-C^{14} to that from glucose-6-C^{14} was close to unity for slices from brain cortex in either the presence or absence of ethanol and its metabolites, and hence no evidence for a functioning hexose phosphate oxidative pathway could be demonstrated. KATZ and WOOD[8] have pointed out the difficulties that arise when an attempt is made to calculate from tracer studies the *percentage* of glucose that is metabolized *via* the glycolytic pathway as compared with that *via* the hexose monophosphate pathway. No such attempt was made in this study. The question these experiments were designed to answer was whether there is any evidence that glucose *can be* metabolized by brain *via* the hexose monophosphate shunt under normal conditions or during ethanol intoxication. The results show the answer to be negative, and this reposes the question of the significance of the observable activities of the glucose-6-phosphate and 6-phosphogluconate dehydrogenases in brain. One possible explanation would invoke a carry over of these two enzymes from an embryologically functional phosphogluconate pathway operating at low oxygen tension. The young, but not adult, brain synthesizes its own cholesterol and other lipids *in situ* and this would permit efficient reoxidation of TPNH formed by the dehydrogenases of the phosphogluconate pathway without a requirement for oxygen.

Oxidation of glucose-1-C^{14} and glucose-6-C^{14} by rat brain slices

	No. of rats	% Conversion of labeled glucose to $C^{14}O_2$		$\frac{C^{14}O_2 \text{ from gl-1-}C^{14}}{C^{14}O_2 \text{ from gl-6-}C^{14}}$
		Glucose-1-C^{14}	Glucose-6-C^{14}	
Controls	5	1.79 ± 0.28	1.60 ± 0.06	1.12
Ethanol-treated	4	2.54 ± 0.47	2.08 ± 0.32	1.22

Slices of cerebral cortex (350 mg) incubated with shaking at 37°C for 90 min in presence of 20 mg glucose containing 0.2 μC of either glucose-1-C^{14} or glucose-6-C^{14} in 5 ml Krebs-Ringer bicarbonate containing 0.1*M* KCl. 'Ethanol-treated' preparations contained in addition 12.5 mg ethanol, 25 μg acetaldehyde and 250 μg acetate. Gas phase, 95% O_2–5% CO_2. Results are expressed as means ± standard error.

Résumé. L'auteur a repris la question de l'existence d'une voie oxydative fonctionnelle directe pour la glucose dans le cerveau adulte et constaté qu'elle ne peut être décelée ni dans des conditions normales ni lors d'une intoxication du sujet par l'étanol.

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The Short-term Effects of a Single Dose of Erythropoietin upon Reticulocytes in Starved Rats[1]

Despite the voluminous literature describing the effects of erythropoietin[2–4], its site of action has not been clearly established. Some authors have suggested that erythropoietin acts exclusively upon the stem cell with the resultant production of increased numbers of erythrocytic precursors[5,6], while others have contended that this material may also exert its action by increasing cellular division among nucleated erythrocytes that have advanced well beyond the stem cell stage[3,7]. Measurement of the rapidity of the reticulocyte response should furnish some information as to which of these views is correct. If erythropoietin acts exclusively upon the stem cell, following its injection at least one entire maturation cycle of nucleated red blood cells would have to be completed before there would be any evidence of the delivery of newly-formed reticulocytes into the blood. This would

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