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STRESS AND THE MECHANISM OF THE DIABETOGENIC ACTION OF PITUITARY GROWTH HORMONE

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The alarm stimulus or stressor is the agent able to produce the Stress Syndrome of Selye. The stress is characterized by the hypothalamic neuro-endocrine activation which is a transitional response that modifies the hormone and metabolic homeostasis (heterostasis of Selye). The diabetogenic potentiality of this stress response was suggested by the hyperglycemia and hypersecretion of glucocorticoids of the alarm reaction.[1] Nevertheless, in experiments of rats with benign pancreatic diabetes mellitus submitted to repeated formaldehyde stress during one week, Ingle and Nezamis demonstrated an improvement of the diabetic state.[2] This paradoxical result prompted us to a rather long series of experiments trying to clarify its contradiction with the clinical observation which had shown an aggravation of the diabetic patient suffering from physical or psychological stress.[3,4,5] If there was an opposite result, on the same matter, between the animal and human experimentation, it was important to reinvestigate the influence of stress on diabetes, trying to find a biologic model that could permit to demonstrate a diabetic disturbance consecutive to the stress.

Re-study of the Ingle and Nezamis publication[2]. We have discussed in detail[5] the interesting problem generated by the experiment of those autors. We will summarize the following points: a) although the data of the paper did not permit the statistical calculation

of the results, it appears that with two daily doses of 1.0 ml of 1.5% formaldehyde, they really obtained an improvement of the diabetic state during the treatment period (Fig. 1); b) we do confirm that 2% formaldehyde 1.0 ml daily produced thymic-lymphatic involution and adrenocortical stimulation,[1] i.e. ACTH discharge with glucocorticoid hypersecretion; c) however with formaldehyde[6] we could not induce the appearance of alpha$_2$-inhibitor,[7,8] a growth hormone dependent insulin antagonist[9] (Fig. 2), localized in alpha$_2$-glycoprotein;[10] d) and we could not induce the "post-stress diabetic response" (PDR) in the 80% pancreatectomized rat,[6] as it was produced with restraint plus cold[11] (Fig. 3); e) formaldehyde did not stimulate the pituitary growth hormone discharge, as cold stressor did after 5 minutes of exposure.[12] Table 1 and 2 summarizes the results obtained after local and systemic stress under different experimental conditions.

Consequently it was concluded that a dissociation of the hypothalamic activation against local stressor (formaldehyde) and systemic stressor (restraint plus cold) does exist. (Fig. 4) In the first case ACTH was stimulated, whereas in the second case, ACTH together with growth hormone, were hyperdischarged[Q]. Such dissociation will explain that the PDR, characterized by transient hyperglycemia, glycosuria and appearance in the rat of alpha$_2$-inhibitor after stress, did not occur in the local stress, since the PDR is a STH-dependent reaction, (Table 1). Our observations with formaldehyde were confirmed by various other local stressor such as turpentine, croton oil or subcutaneous implantation of cotton pellets (aseptic inflammation).[6] (Table 2) Even local stress/by turpentine superimposed to systemic stress could not

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[Q] Somatotropin hormone (STH) will be used as synonymous of growth hormone.

increase the intensity of the PDR (Table 3).

Through these results we thought that formaldehyde could provoke the amelioration of the rat diabetic state by a formaldehyde "drug" action, independent of the aggressive-stressor effect of the formaldehyde molecule. It was known that Urotropin (hexamethylene-tetramine), a condensation of formaldehyde in the presence of an excess of ammonia,[13] potentiated the hypoglycemic effect of insulin when it was added "in vitro" to insulin (hexamine-insulin).[14] Since a release of the formaldehyde from Utropin could occur in the blood or in the beta-cell of the Langerhans islands, we tried to produce an "in vitro" formaldehyde insulin (forminsulin). (Fig. 5) summarizes the results showing a potentiation of the insulin i.v. injected to rabbits either with hexamine-insulin or forminsulin. Not only was the time effect of 1 I.U./kg increased but so was the frequency of the hypoglycemic shocks (Table 4). This result suggested the possibility that in the Ingle-Nezamis experiment some of the subcutaneous formaldehyde leaked to the blood and bound the scant insulin of the partial pancreatectomized rat, producing forminsulin and potentiating the insulin effectiveness. Since formaldehyde did not stimulate pituitary STH,[12] alpha$_2$-inhibitor was not generated and the PDR was absent. The greater improvement of the stressed diabetic rat after adrenalectomy,[2] could be the result of the glucocorticoids elimination with the suppression of their diabetogenic effect. Thus adrenal extract replacement, made in the adrenalectomized rat by Ingle and Nezamis, might trigger the permissible effect of glucocorticoids only, without imitating what could be expected during the hypersecretion of adrenal glucocorticoid of the stress.

Local ans Systemic Stress

As we mentioned before there is an important difference between Local and Systemic stress as far as alpha$_2$-inhibitor response is concerned. Our insulin antagonist, tentatively

identified with alpha$_2$-neuroaminoglycoprotein,[10] did not appear after Local stress. On the other hand it is known that several blood glycoproteins have been found increased during inflammation, necrosis and proliferative processes.[15,16,17,18,19,20]

Among these glycoproteins we were especially interested in the appearance of a specific serum alpha$_2$-glycoprotein during subcutaneous inflammation.[18,19] Its appearance was mediated by the adrenals and required tissue injury and 8-12 hours for obtaining adequate titers, whereas alpha$_2$-inhibitor appeared 2-3 hours after initial stress time,[11] with apparently no physical damage. Moreover in the rat turpentine abscess produced the appearance of plasma glycoproteins even in the absence of the pituitary gland,[21,22] a fact not observed with the specific post-inflammatory alpha$_2$-glycoprotein[18] or with the alpha$_2$-inhibitor.[9] Thus, the appearance of alpha$_2$-inhibitor after a systemic stress acquired specificity (Table 5). At the present time we do not know the functional role played by the above mentioned glycoproteins.

Our working hypothesis of liver production of the alpha$_2$-inhibitor is coincident with several demonstrations including experiments in isolated liver[26], supporting the idea that the stress elevation of glycoproteins is the result of an increased glycoprotein synthesis in the liver.[23,24,25]

Impact of stress upon diabetes

The systemic stress, through a functional change in the set point of the hypothalamus, produces a prolonged hypersecretion of STH.[28,29] In our working hypothesis this hormone stimulates in the liver the alpha$_2$-glycoproteins synthesis and introduces in these proteins the active chemical terminal group, originating the biologic anti-insulin activity (alpha$_2$-inhibitor). This will produce a diminished uptake of glucose by the muscle[7,8] and fat,[30]

leaving more circulating glucose and increasing the glycemia. The competitive action of alpha$_2$-inhibitor is visualized at the cellular level through a direct antagonism toward the glucose transport. Alpha$_2$-inhibitor is not neutralized "in vitro" by insulin, but it would act on the substrate.[31] If the pancreas has a normal insulin reserve and is able to hypersecrete insulin under the stimulus of the hyperglycemia, the alpha$_2$-inhibitory glucose interference would be counterbalanced. Therefore, keto-acidotic coma, without stopping or reducing insulin administration is understood as a complete predominance of STH and alpha$_2$-inhibitor as a final pathophysiologic response due to a severe systemic stress.[5] This could explain why 70% of our keto-acidotic coma were observed in diabetic patients still receiving their daily insulin dosage but under different stressful stimuli where infections occupied the first place.[32] This could also explain why such coma is not observed in acromegalia of Cushing diabetes, where insulin is maintaining the secretory capacity. With this comprehensive point of view, the Stress Syndrome takes a more enriched pathophysiologic perspective having the potentiality to produce either an unbalance of a treated diabetes or the emergence of diabetes in some apparent normal borderline prediabetic states.

Partial pancreatectomy and chlorpromazine (CPZ) in the study of the experimental post-stress diabetic response (PDR)

The rather rapid disappearance of alpha$_2$-inhibitor after stress,[11] suggested an insulin hypersecretion which avoided the full manifestation of PDR, with regulation of hyperglycemia and prevention of glycosuria. The reduction of the insulin secretion by means of the 80% pancreatectomy, supported this assumption and put into evidence the potential diabetogenic power of systemic stress. Submitting to systemic stress this non-

diabetic 80% pancreatectomized rat, it was observed a full post-stress diabetic response.[11] In the model of the intact-normal rat treated with chlorpromazine (6.9 mg/100 g) plus restraint, a PDR was also obtained. In this last model alpha$_2$-inhibitor was increased in the suprahepatic blood and this increment was not suppressed by acute adrenalectomy.[33,34] (Fig. 6 and 7).

Pharmacologic prevention of the PDR. The above 2 models have opened an anti-stress investigation which is now being explored at different levels of the neuro-endocrine system. Fig. 8 gave a schematic general picture on this project. Until this moment anti-catecholamines, anti-serotonins and drug agents stimulating insulin release are under study. We can advance that low dosage of chlorpromazine (0.1-0.05 mg/100 g) had a significant protection on the PDR of the 80% pancreatectomized rat submitted to restraint and cold stress (Fig. 9); that the anti-serotonin oxypertine[Ω] in doses of 50-100 µg/100 g of rat, gave no conclusive results, whereas glipizine[Ω], a sulfonylurea derivative of rapid action,[40] prevented 100% the PDR in doses of200 µg/100 g. Thus the study of point 18 of our scheme on neuro-endocrine participation in the PDR (Fig. 8), i.e. improvement of insulin release from the remnant of rat's pancreas, has a promising beginning (Fig. 10).

Speculation on alpha$_2$-inhibitor of man and rat. Importance of the systemic stress

It is of interest to speculate on the difference of alpha$_2$-inhibitor in human and rat. In the normal man, it is

Ω Kindly supplied by Winthrop Laboratory and by Carlos Erba, respectively.

spontaneously present[7,8] and disappears after hypophysectomy and reappears after h-STH administration,[9] whereas in the rat alpha$_2$-inhibitor appears only after systemic stressful conditions or after r-STH administration.[11] Does this mean that man is living under almost permanent stress adaptive regulation? or, as a result of such adaptive effort the human specie developed not only its own STH but required higher STH secretion favoring the functional diabetogenic deviation? Could this interpretation explain to some extent the high percentage of diabetes mellitus that exists throughout our "wonderful" world? At the present time it is imposible to answer properly these questions. But since I am biased for being immersed in the subject, I have the tendency to accept it and to work mentally with the influence of stress on the genesis and evolution of this peculiar and important metabolic disease.

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TABLE 1.

SYSTEMIC STRESS AND POST-STRESS DIABETIC RESPONSE (PDR)

Sprague-Dawley, adult male rat.

Group	Rat condition	Post stress diabetic Response: Hyperglucemia	Glucosuria	Appearance of alpha$_2$-inhibitor in Arterlal blood	Neuro Endocrine Response with increment of :
Without stress	Intact-normal	0	0	0	0
With stress♀	Intact-normal	+	0	+	ACTH + STH[12]
Without stress	80%-Pc	0	0	0	0
With stress♀	80%-Pc	+++	++	++	ACTH + STH
Pentobarbital anesthesia	Intact-normal	+++	++	++	STH without ACTH[36,37]
Ether anest.	intact-normal	++	0	0	ACTH without STH[38]
Restraint + CPZ♀♀	intact-normal	+++	+++	+	STH[39] + ACTH
Restraint + CPZ	adrena-lectom.	+++	±	±	STH + ACTH (with no glucocorticoids secretion)
Restraint + CPZ	80%-Pc	++++	++++	++	STH + ACTH
				Ketonuria	
Without stress	diabetic	++++	++++	0	
With stress♀	diabetic	++++	++++	+++	ACTH + STH

♀ Restraint plus cold-17ºC environment during 60 minutes; pentobarbital anesthesia was longer than 3 hours; blood samples, 3 hours after finished the stress or after 3 hours of starting anesthesia.

♀♀ CPZ-chlorpromazine subc. administration: N for each group = 10. Data summarize from experiments of M.E. Kawada, V. Correa, L. Aguilera, A. Ortuzar and D. Videla. 6,11,20.

TABLE 2.

ABSENCE OF DIABETIC RESPONSE AFTER LOCAL STRESS.-

Sprague-Dawley, adult male rat.

Agent	Rat condition	Post-stress Response : Hyperglucemia	Glucosuria	Alpha$_2$-inhibitor (arterial)	Neuro-endocrine Response
ASEPTIC INFLAMMATION					
Formaldehyde	intact-normal	0	0	0	ACTH without STH[12]
Formaldehyde	80%-Pc		0	0	ACTH withour STH[12]
Turpentine	intact-normal	0	0	0	ACTH
Turpentine	80%-Pc	0	0	0	ACTH
Croton oil	intact-normal	0	0	0	ACTH
Subc. cotton pellet implant	intac normal	0	0	0	ACTH
SEPTIC INFLAMMATION					
Subc. Staphilococcous aureous	intact-normal	0	0	0	?
Subc. Staphilococcous aureous	80%-Pc	0	0	$\pm$ (?)	?

N for each experimental group = 6 to 8 rats.
Data summarize from experiments done in collaboration with M.E. Kawada, R. Capponi, C. Airaudo, S. Kaliski, F. Uyevich, R. Espinoza. Staphilococcous from human inflammation kindly supplied by Prof., M. Rodríguez, Dept. of Cellular Biology, Institute of Biological Science, Catholic University of Chile, Santiago.

TABLE 3.

LOCAL STRESS SUPERIMPOSSED TO SYSTEMIC STRESS, in normal-intact Sprague-Dawley rat, male, 180 g.

	0'	60'	120'	180'	240'
CONTROL					
Glucosuria	0	0	0	0	0
Glucemia	97 ± 7	-	-	132 ± 12	-
Inflammation					
Glucosuria	0	0	0	0	0
Glucemia	115 ± 9	-	-	140 ± 12	-

N = 5 for each group. Inflammation produced by suplantar 0.1 ml turpentine. Systemic stress provoked by restraint plus cold enviroment -17ºC. during 60 minutes.

TABLE 4.

FRECUENCY OF HYPOGLYCEMIC SHOCKS AFTER 2 HOURS OF HEXAMINE-INSULIN OR FORMINSULIN I.V. ADMINISTRATION.

Group	Nº of rabbits	Shocks :			
		Nº	%	severe[Ω]	fatal
INSULIN CONTROL	15	0	0	0	0
INSULIN + UROTROPIN (hexamine-insulin	16	9	56	2	1
INSULIN + FORMALDEHYDE (forminsulin)	12	10	83	0	1

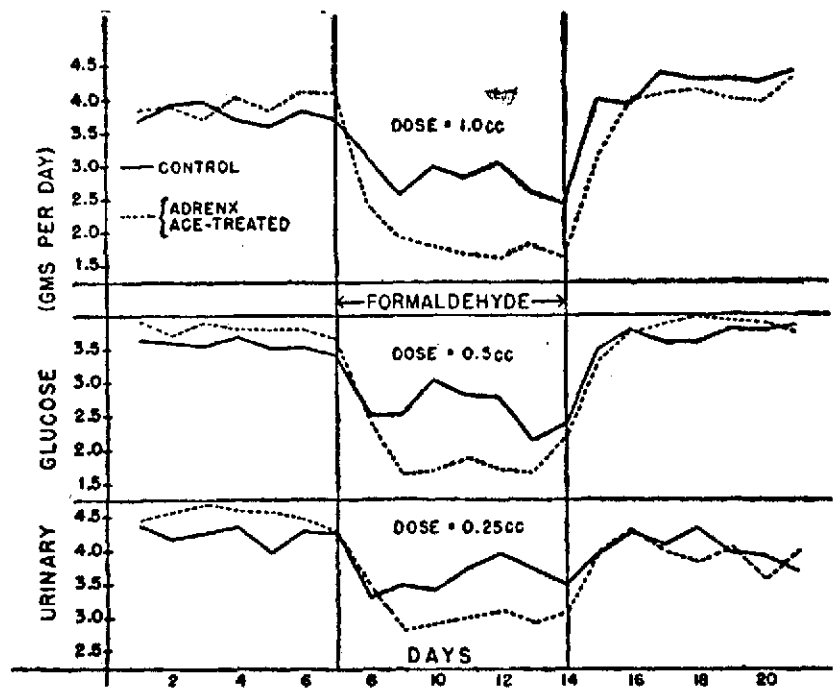
Ω The intensity of the shock was so pronounced that i.v. administration of 50% glucose solution was required; fatal cases occured in spite of this treatmen. The difference between hexamine-insulin and forminsulin was statistically significant. These results correspond to the experiments presented in Fig.4.

TABLE 5.

Non-response of alpha$_2$-inhibitor after Local Stress as compared with other blood glycoproteins (GP) which have a positive response as reported under equivalent experimental conditions.

Substance	Human or rat condition	Local damage	Blood increment	Reference
Serum - GP	Normal-intact rat	Inflammat. necrosis	+	15,16,17
Serum - GP	hypophysectomized rat	inflammat. (turpentine)	+	20,21
Serum - GP	Patient	bone fracture	+	27
Serum - $\alpha_2$globulins	Patient	bone fracture	+	27
Acute-phase α_2 globulin	normal-intact rat	inflammat. (turpentine)	+	20
Specific α_2-GP	normal-intac rat	inflammat. (subc. cotton pellet implant)	+	18, 26
α_2-inhibitor ($_2$-GP)	normal-intact rat	inflammat. (formaldehide, turpentine, croton oil, cotton pellet)	0	6
α_2-inhibitor	80% pancreatectomized rat	formaldehyde,	0	6
		turpentine	0	

Most of the GP appeared after 24 hours, whereas alpha$_2$-inhibitor 2-3 hours post-stress only after systemic stress. Turpentine and cotton pellet inflammation were studied at 3, 6, 24, 48, and 196 hours after the initial time. In no instance a positive alpha$_2$-inhibitor response was observed.



Legend of figures

Fig. 1 Improvement of diabetes mellitus of rats submitted to stress by daily formaldehyde injections, according to Ingle and Nezamis.[2] Daily glucosuria was used as the most characteristic final sign of the carbohydrate metabolic disturbance. Continuous line = control; dotted line = adrenalectomized rat treated with cortico-adrenal extract. The diabetes was produced by partial pancreatectomy under force-fed condition and without insulin administration.

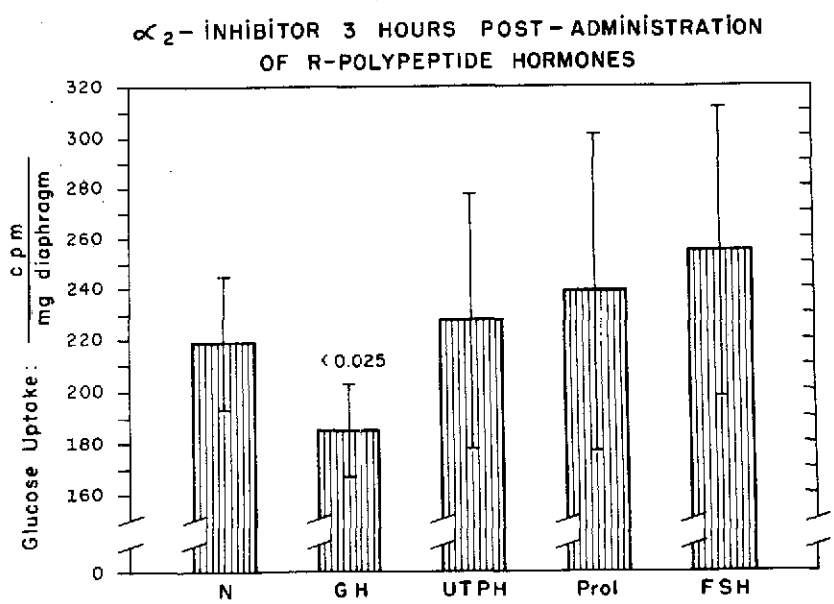


Fig. 2 The bioassay of glucose uptake by rat hemidiapharagm demonstrated that only growth hormone (GH) produced in the rat the appearance of alpha$_2$-inhibitor with inhibition of glucose uptake. The hormones were i.m. administered to Sprague-Dawley male rats (180)g, in a single dose of 100 µg in 0.1 ml of Gey buffer per rat. Mean ± SD from 6 observations; pool of plasma of 3 rats for each determination; 10 µg of alpha$_2$-glycoprotein (alpha$_2$-GP) per ml of buffer. N = normal GP from normal rat injected with Gey buffer; GH = growth hormone; UTPH = uterotrophic placental hormone; Prol = prolactin; FSH = follicle-stimulating hormone. Figure drew from data of Vargas, Bronfman and Kawada.[11]

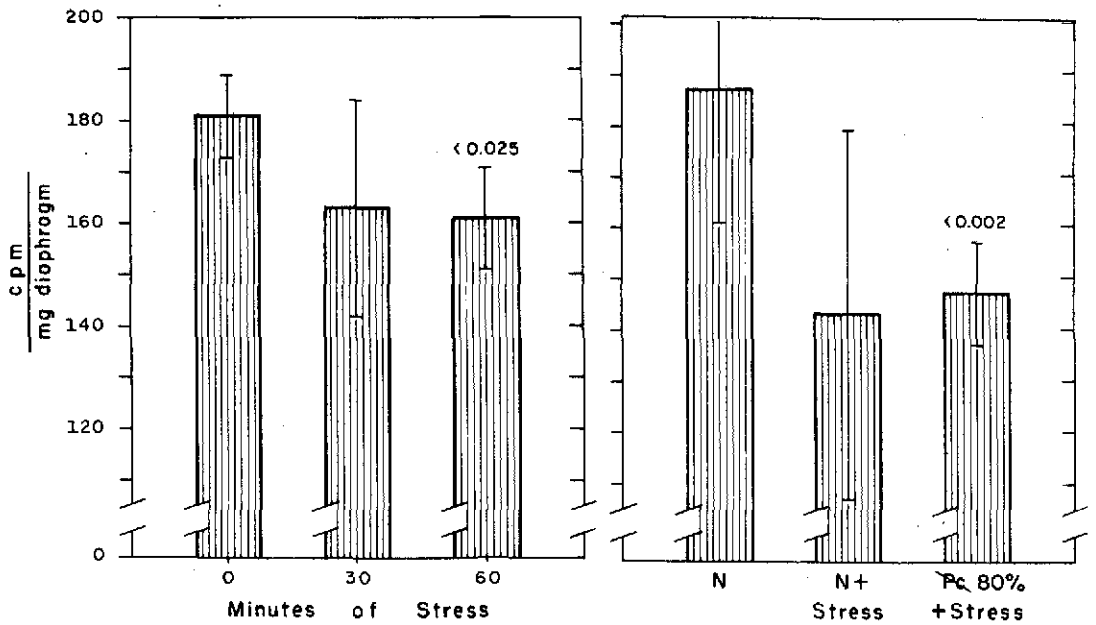


Fig. 3. Production of plasma alpha$_2$-inhibitor after 60 minutes of systemic stress in intact-normal rat (left side) and after 45 minutes in 80% pancreatectomized rat. Only in the latter case it was accompanied with glucosuria. Mean ± SD from 8 observations (other details as Fig. 2). Figure drew from data of Vargas, Bronfman and Kawada.[11]

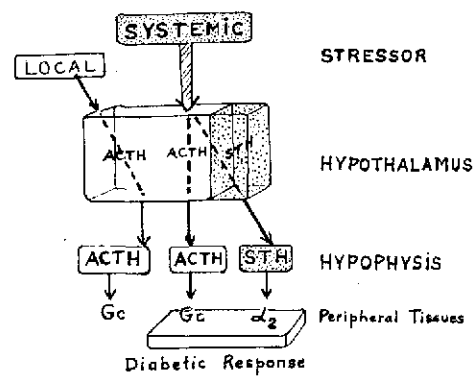


Fig. 4. Schematic representation of two hypothalamic compartments reacting in a separate way under local or systemic stressor. Only the latter provokes the appearance of alpha$_2$-inhibitor with the post-stress diabetic response (PDR).

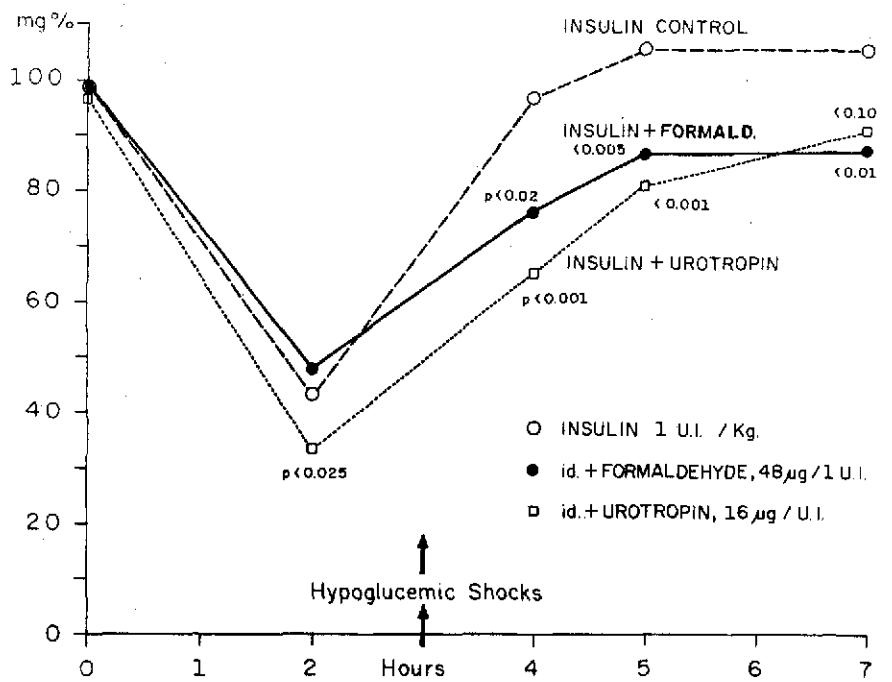


Fig. 5. Significant potentiation of insulin hypoglucemia when insulin was treated "in vitro" with formaldehyde. The control group (1 I.U. kg, i.v.) restored the glucemia at 4 hours, whereas formaldehyde-insulin maintained its effect at 7 hours (P 0.01).
Insulin hypoglucemic test made according the North American Farmacopea, in adult rabbits, after 16 hours of fasting. Insulin (24 I.U./mg) kindly supplied by Connaught Laboratories of Toronto, Canada. Data re-studied and statistical calculated from experiments done in our laboratories by Oscar de Gatica.[35]

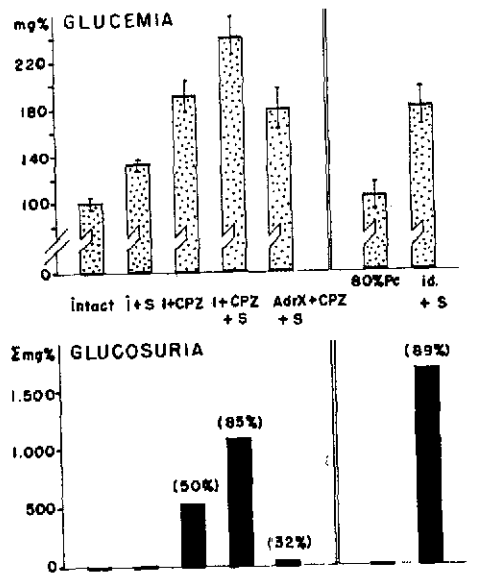


Fig. 6. Full PDR with chlorpromazine (CPZ) plus restraint alone. Normal-intact adult Sprague-Dawley received 6.9 mg/100 g of CPZ before the restraint stress of 60 minutes. The glucemia were calculated at 3 hours post-stress, but the glucosuria correspond to the total average excreted during the whole period of 3 hours. On the right side, similar restraint stress without CPZ in 80% pancreatectomized rat. In this series of experiments, alpha$_2$-inhibitor was present in every instance except in intact or 80% pancreatectomized without stress. According to Vargas and collaborators, not published.

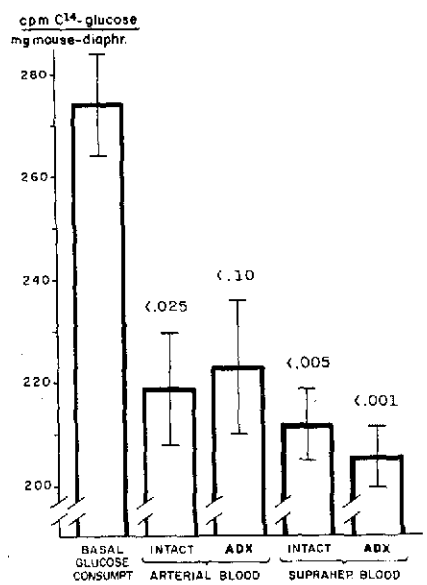


Fig. 7. Determination of alpha$_2$-inhibitor in suprahepatic blood from adrenalectomized stressed rats. The data depicted in this figures correspond to the experiments shown in Fig. 6.

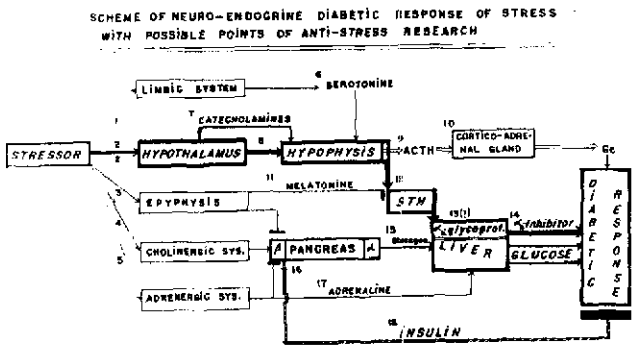


Fig. 8. Theoretic dynamic interpretation of the post-diabetic stress mechanism. Possible points of prevention.

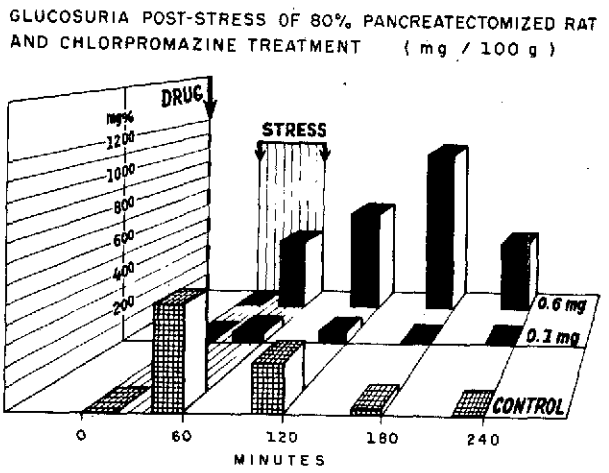


Fig. 9. Partial protection of the PDR in the 80% pancreatectomized rat by means of chlorpromazine (CPZ) treatment. Only doses of 0.1 mg/100 g of CPZ per rat decreased the glucosuria down to an 84%

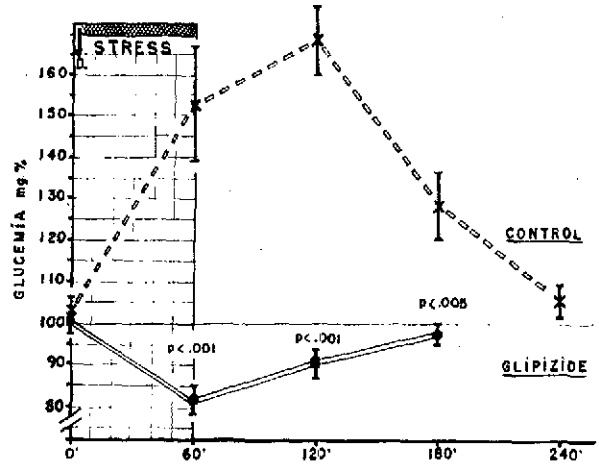


Fig. 10. Total protection of PDR in 80% pancreatectomized rat treated with glizipida, a sulfonylurea derivative (N-4(5-methyl-pyrazin-2-carboxiamide-ethyl)benzensulfonyl N'cyclohexylurea). Doses of 200 µg/100 g/rat affords a complete neutralization of the hyperglucemia observed in the stress response. A second turn of similar experiments using the interchanged of the same groups (the control received the drug and vice-versa), confirmed these results where all the mean points of the curve were statistically significants. Seminar 266-S, Inst. Sci. Biol., C. Varela, X. Solovelles, V. Correa and L. Vargas, 1975.