Retraction Notice

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History
Expression of Concern:
Date(yyyy-mm-dd): none Link:
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Comment:
The paper does not meet the standards of "Food and Nutrition Sciences".

This article has been retracted to straighten the academic record. In making this decision the Editorial Board follows COPE's Retraction Guidelines. The aim is to promote the circulation of scientific research by offering an ideal research publication platform with due consideration of internationally accepted standards on publication ethics. The Editorial Board would like to extend its sincere apologies for any inconvenience this retraction may have caused.

Editor guiding this retraction: Prof. Thomas Müller (EiC of NM)

Please see the article page for more details. The full retraction notice in PDF is preceding the original paper, which is marked "RETRACTED".

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Anorexia Nervosa versus Hyperinsulinism: The Two Opposite Faces of the Coin

—Therapeutic Effects of Neuropharmacological Manipulations

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ABSTRACT

We demonstrated that anorexia nervosa (AN) was underlain by overwhelming adrenal sympathetic activity which annuls neural sympathetic branch of the peripheral autonomic system (ANS). This physiological disorder is responsible for the gastrointestinal hypomotility + hyperglycemia + raised systolic blood pressure + raised heart rate and other neuroendocrine disorders. Thus we prescribed neuropharmaclogical therapy addressed to revert central nervous system + ANS disorder, in order to normalize both clinical + neuroendocrine profiles. We measured blood pressure, heart rate, circulating neurotransmitters, noradrenaline, adrenaline, dopamine, platelet serotonin, plasma serotonin during supine resting + one-minute orthostasis + five min exercise test before and after 1, 2 and 3 months of treatment with amantadine, a drug which abrogate adrenal sympathetic activity by acting at the C1(Ad) medullary nuclei, responsible for this peripheral sympathetic activity. We found that the drug eliminated AN symptoms since the first oral dose. Normalization of ANS plus cardiovascular parameters was registered within the first days of therapy. Abrupt and sustained increases of the noradrenaline/adrenaline plasma ratio + disappearance of abnormal plasma glucose rises were registered throughout the 3 months lasted the trial. Significant and sustained body weight increases were registered in all the cases. No relapses were observed in any case. We ratified our previous findings showing that the anorexia syndrome depends on hypomotility of the gastrointestinal tract plus de hyperglycemia associated with the hyperactivity of the adrenal sympathetic activity. In addition, we afford exhaustive evidence showing that the hyperglycemia + adrenal sympathetic overactivity syndrome and the hypoglycemia + the neural sympathetic overactivity disorder depend on the predominance of the C1(Ad) medullary + adrenal glands axis and the A5(NA) + neural sympathetic axis, respectively. Both syndromes are successfully treated with neuropharmacological manipulations.

Keywords: Amantadine; Anorexia Nervosa; Adrenal Sympathetic Activity; Hyperglycemia; Hyperinsulinism; Neural Sympathetic Activity

1. Introduction

We demonstrated that doxepin, a drug which inhibits the uptake of serotonin (5-HT) was able to normalize patients affected by the hyperinsulinism and hypoglycemia syndrome [1]. Furtherly, we showed that amantadine, (a NMDA glutamate antagonist), was able to enhance insulin secretion and minimize plasma glucagon levels [2-8]. Considering that both metabolic and hormonal effects were paralleled by the attenuation of neural sympathetic and adrenal sympathetic activity, respectively, we inferred that neuropharmacological drugs able to attenuate the hyperactivity of the C1(Ad) medullary nuclei [3-8], might be powerful therapeutic tools addressed to treat all types of adrenal sympathetic predominance, including the AN syndrome.

According to the above and with our previous demonstration showing that the AN syndrome is underlain by maximal adrenal sympathetic overactivity [9], we decided to test the possible therapeutic effects of amantadine, a NMDA antagonist that interferes with the excitatory glutamate axons at the medullary C1(Ad) nuclei, in 22 patients affected by this pathophysiological disorder.

2. Methods

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained after the purpose, nature, and potential risks had been explained to the subjects. The experimen-

tal protocol was approved by the ethical committee of the "Fundación Instituto Medicina Experimental".

2.1. Patients

The study included 22 female AN patients (10 restricted type and 12 binge-eating type) before treatment [9], and after three months of amantadine (100 mg daily) treatment. The diagnoses were made according to DSM-IV criteria. Mean age ± standard deviation (SD) of the AN patients was 22 ± 6.4 years and weight 70% ± 10.1% of ideal body weight, according to Metropolitan Life Insurance Company tables. All patients were extensively evaluated (physically, endoscopically, radiologically, biochemically, bacteriologically, and immunologically) in order to rule out any other physical illness. Exclusion criteria included pregnancy, lactation, smoking, and alcohol abuse. Patients did not take any medication for 15 days prior to the beginning of the study.

Measurement of blood pressure (BP) and heart rate (HR) as well as drawing of blood samples were performed simultaneously. Supine BP measurements were taken in a standardized fashion using appropriate-sized cuffs and a random-zero mercury sphygmomanometer. All measurements were taken in accordance with a previously published protocol [10]. Blood samples for plasma neurotransmitter determinations were obtained simultaneously with BP and HR measurements through a heparinized catheter, inserted into the antebrachial contralateral vein 15 minutes before the first BP and HR measurements. Plasma noradrenaline, adrenaline, dopamine, free serotonin (f5-HT) and platelet serotonin (p5-HT) levels were assessed during supine-resting, one-minute orthostasis, and after five-minutes of moderate exercise. All tests were performed on subjects after 10 hours of fasting. A physician in constant attendance noted any symptoms reported by the subjects.

2.2. Analytic Methods

Noradrenaline, adrenaline, dopamine, plasma f5-HT, and p5-HT levels were measured. For all parameters, the samples were assayed in duplicate and all determinations were made simultaneously. We used reverse-phase, ion-pair high performance liquid chromatography with electrochemical detection for the measurement of monoamines. Optimization of chromatographic conditions and attainment of adequate quantification parameters allowed us to maximize sensitivity and reproducibility.

Blood for catecholamine and serotonin assays was transferred to plastic tubes, each containing 20 mg of ethylenediaminetetraacetic acid (EDTA) and 10 mg of sodium bisulphite/mL in solution. The tubes were carefully inverted and placed on ice. The blood was promptly centrifuged at 600 rpm for 15 minutes at 4˚C in order to obtain platelet-rich plasma. Two milliliters of platelet-rich plasma, obtained for determination of p5-HT, were taken and stored at –70˚C until assayed. The remaining blood was again centrifuged at 7000 rpm. The supernatant, platelet-poor plasma, was divided into two portions for determination of catecholamines and f5-HT, after which the portions were stored at –70˚C until assayed.

2.3. Reagents and Standards

Noradrenaline, adrenaline, dopamine, serotonin creatinine sulfate, dihydroxybenzylamine, sodium octyl sulfate, dibutylamine, acid-washed aluminum oxide, KH2PO4, citric acid, and EDTA were purchased from Sigma-Aldrich (St Louis, MO). Microfilters were purchased from Whatman Inc. (Florham Park, NY) through Merck SA, (Caracas, Venezuela). Acetonitrile and 2-propanol were obtained from Merck SA. Glass-distilled water was deionized and filtered through a Millipore Milli-Q reagent grade water system (Bedford, MA). Solvents were filtered through a 0.2 µm Millipore filter and were vacuum de-aerated. Standard solutions (1 mmo1/L) were prepared in 0.1 mo1/L perchloric acid and diluted to the desired concentration.

2.4. Equipment

Liquid chromatography was performed using a Waters 515 HPLC pump (Waters Milford, MA) equipped with a Rheodyne valve injector 7125i, which was fitted with a 50 µL sample loop (Rheodyne; Berodine, Berkeley, CA). A 15 cm × 4.6 mm inner diameter Discovery C18 column packed with octadecyl silane 5 µm particles was preceded by a column prefilter of 2 µm porosity, both from Supelco/Sigma-Aldrich. The detection system was a 460 electrochemical detector (Waters Corporation, Milford, MA). The potential of the glass carbon working electrode was set at 0.61 V versus the silver-silver chloride (Ag-AgCl) reference electrode for detection of catecholamines and 0.70 V versus the Ag-AgCl for detection of indolamines. The chromatograms were registered and quantified using Empower software from Waters Corporation. The results were corrected for the volume of EDTA added.

2.5. Analytical Assays

2.5.1. Plasma Catecholamines

The assay was performed by extraction of the catecholamines onto 20 mg of alumina followed by elution with 200 µL of 1.0 mo1/L $HClO_4$ using regenerated cellulose microfilters of 0.2 µm pore size purchased from Whatman Inc. We calibrated the instrument with standard plasma; after incubation with acid-washed aluminum oxide, a plasma pool of free catecholamines was processed similarly to the plasma samples, but 20 µL of a standard solution of noradrenaline, adrenaline, and dopamine (50, 25, and 25 ng/mL, respectively) was added to the plasma

pool. Both the standard plasma and the sample plasma were supplemented with 20 µL of internal standard (100 ng/mL of dihydroxybenzylamine). The mobile phase was KH2PO4 6.8045 g/L, EDTA 0.1 g/L, and di-Nbutylamine 100 µl/L. Sodium octyl sulphate was added as an ion-pair agent at a concentration of 0.6125 g/L, with the pH adjusted to 5.6. The flow rate was 0.4 mL/min. The sensitivities of this method for noradrenaline, adrenaline, and dopamine, respectively, were 6.4, 5.8, and 2.0 pg/mL. The intra-assay coefficients of variation were 2.8%, 4.0%, and 4.0%, respectively. The interassay coefficients of variation were 6.7%, 4.5%, and 4.3%, respectively.

2.5.2. Plasma Indolamines

After sonication of platelet-rich plasma to disrupt the platelets (Ultrasonic Liquid Processor, Model 385; Heat Systems Ultrasonics Inc., Farmingdale, NY), both platelet-rich and platelet-poor plasma were processed in the same way, *i.e.*, 200 µL of 3.4 mol/L perchloric acid and 50 µL of 5-hydroxytryptophan solution (114.5 µg/mL) as internal standard, were added to 1 mL of plasma vortexed and centrifuged at 10,000 rpm for 15 minutes at 4˚C. The supernatant was filtered through a 0.22 µm membrane (Millipore) and 10 µL was injected into the column. Calibration runs were generated by spiking blank platelet-poor plasma with 50 µL of a solution containing 5-HT (10 µg/mL) and 50 µL of 5-hydroxytryptophan (114.5 µg/mL). This standard plasma was processed in the same manner as the samples. The mobile phase was citric acid 3.8424 g/L, sodium acetate 4.1015 g/L, EDTA 0.100 g/L, di-N-butylamine 100 µl/L, and 30 ml/L of 2-propanol. Sodium octyl sulphate was added as an ion-pair agent in a concentration of 4.25 mg/L with a pH of 5.0. The flow rate was 0.610 mL/min. The sensitivity of the method for serotonin was 0.1 ng/mL. The intra-assay coefficients of variation for p5-HT and f5-HT were 6.2% and 8.7%, respectively.

2.6. Statistical Methods

Results are presented as the mean ± standard error of measurement (SEM). Multivariate one-way analysis of variance (ANOVA) with repeated measurements, and correlation coefficients (exploratory factor analysis) were used. Dbase Stats (TM) by Ashton Tate and Statview SE ± Graphics by Abacus were used for the statistical analysis.

3. Results

We previously demonstrated that there are not significant neuroendocrine + neuroautonomic differences between the two clinical types of AN (restricted and binge-eating type) [9]. The results presented in this therapeutical trial showed that a low dose of amantadine (100 mg/daily), a drug which abruptly suppresses adrenal sympathetic activity [9,11], was able to annul AN symptoms when it is administered 45 minutes before the main meal, and in addition, when it is administered 45 minutes before the oral glucose tolerance test (manuscript in preparation). Patients were able to eat all types of foods and recovered their normal body weight. Normalization of cardiovascular parameters [enhancement of diastolic blood pressure (DBP) and reduction of systolic blood pressure (SBP) and heart rate (HR)] were also registered in all cases. Namely, the present research study ratified that anorexia nervosa syndrome is underlain by the absolute, overwhelming predominance of the adrenal sympathetic branch which abrogates neural sympathetic activity. This pathophysiological disorder includes symptoms at all type of levels (cardiovascular, digestive, metabolic, endocrine, respiratory, etc.) as well as psychological and neuroautonomic disturbances.

3.1. Cardiovascular Parameters

Neither systolic BP nor diastolic BP showed significant variations during orthostasis or after moderate exercise in AN patients. However, differential pressure showed a significant increase during orthostasis before treatment but not after amantadine treatment. HR showed significant and progressive rises during both orthostasis and exercise periods before but not after amantadine treatment (**Table 1**).

3.2. Catecholamines

Plasma noradrenaline showed significant and progressive increases during orthostasis and exercise in the two groups. However, the noradrenaline values and their increases were significantly higher after amantadine therapy. In addition, adrenaline showed important and significant increases during orthostasis and exercise in the AN patients before treatment but not in treated patients. Plasma dopamine levels showed a significant increase during orthostasis in non treated patients but not in treated patients (**Table 1**).

3.3. Indolamines

p5-HT did not show any significant variation in before or after treatment. Plasma f5-HT, (e.g. outside the platelets) showed mean basal values which were greater before treatment and showed progressive and significant decreases after amantadine treatment. Significant correlations amongst the different physiologic and neurochemical variables during rest, orthostasis, and after moderate exercise are shown in **Table 2**.

4. Discussion

The understanding of the pathophysiology of the AN syndrome requires the information dealing with the hyperactivity of the adrenal sympathetic branch [9,12,13] which

Table 1. Systolic, diastolic blood pressure (SBP, DBP), heart rate (HR), noradrenaline (NA), adrenaline (Ad), dopamine (DA), platelet-serotonin (p5-HT) and free serotonin (f5-HT) blood values, at 0 min (resting), 1 min (orthostasis) and 5 min (post-exercise) in 22 patients with anorexia nervosa during symptomatic (pre-treatment period = ANs) and during asymptomatic period (three months after treatment with amantadine 100 mg/daily = ANa).

					P values		
		0 min	1 min	5 min	0' vs 1'	0' vs 5'	1' vs 5'
SBP	-ANs	152 ± 5	158 ± 3	171 ± 6	<0.05*	<0.02*	<0.02*
	-ANa	120 ± 3	128 ± 4	132 ± 6	n.s.	n.s.	n.s.
DBP	-ANs	60 ± 3	60 ± 2	61 ± 3	n.s.	n.s.	n.s.
	-ANa	74 ± 4	70 ± 4	76 ± 6	n.s.	n.s.	n.s.
HR	-ANs	71 ± 3	79 ± 4	83 ± 6	<0.02**	<0.01**	<0.01**
	-ANa	66 ± 6	64 ± 4	74 ± 6	n.s.	n.s.	n.s.
NA	-ANs	166 ± 4	169 ± 5	175 ± 5	n.s.	n.s.	n..s.
	-ANa	186 ± 6	214 ± 8	235 ± 7	<0.05*	<0.01**	<0.01**
Ad	-ANs	52 ± 2	67 ± 3	84 ± 4	<0.05*	<0.001***	<0.001***
	-ANa	27 ± 5	30 ± 4	35 ± 3	n.s.	n.s.	n.s.
DA	-ANs	18 ± 1	21 ± 2	23 ± 2	n.s.	n.s.	<0.05*
	-ANa	15 ± 4	20 ± 4	22 ± 5	n.s.	n.s.	n.s.
p5-HT	-ANs	228 ± 19	249 ± 22	225 ± 25	n.s.	n.s.	n.s.
	-ANa	258 ± 31	316 ± 27	308 ± 32	n.s.	n.s.	n.s.
f5-HT	-ANs	3.2 ± 1	13.7 ± 1	24.5 ± 2	<0.001***	<0.001***	<0.001***
	-ANa	2.1 ± 1	2.3 ± 1	3.1 ± 1	n.s.	n.s.	n.s.

Values are mean ± SE; BP in mm/Hg; HR in beats/min; NA, Ad, and DA in pg/ml; p5-HT and f5-HT in ng/ml; (*) $P < 0.05$; (**) $P < 0.02$; (***) $P < 0.001$; n.s. = non significant. Most decimals were omitted.

Table 2. Significant correlations for physiological and plasma neurotransmitter parameters at 0 min (resting), 1 min (orthostasis) and 5 min (post-exercise) in 22 Anorexia Nervosa patients during symptomatic period (pre-treatment period = ANs) and during asymptomatic period (three months after treatment with amantadine 100 mg/daily = ANa).

		SBP	DBP	HR	NA	Ad	DA	p5-HT	f5-HT
ANs	0 min								
HR		0.61*							
Ad		0.66*		0.70*					
DA						0.64*			
f5-HT				0.70*		0.70*			
ANa	0 min								
HR		0.63*							
ANs	1 min								
HR		0.60*							
Ad		0.60*		0.69**					
DA						0.63**			
f5-HT				0.60*		0.69*			
ANa	1 min								
Ad				0.63*					
ANs	5 min								
HR		0.70**							
Ad		0.75**		0.80***					
f5-HT				0.66*		0.68*			

SBP (systolic blood pressure); DBP (diastolic blood pressure); HR (heart rate); NA (noradrenaline); Ad (adrenaline); DA (dopamine); p5-HT (platelet serotonin); f5-HT (free serotonin); (*) $P < 005$; (**) $P < 0.02$; (***) $P < 0.001$.

is responsible for gastrointestinal hypoactivity [9,14-17] SBP + HR enhancement, hyperglycemia, tracheobronchial dilation + hypersecretion, anxiety [18], etc. Neuroendocrine plus metabolic disorders should be also included into this syndrome, whose source is located at the medullary C1(Ad) nuclei, responsible for the peripheral adrenal sympathetic branch [19,20]. The findings presented in this study demonstrating also that an oral dose of amantadine, a NMDA antagonist which annul the firing activity of the C1(Ad) medullary nuclei support our point of view [11]. With respect to this, we found that the drug minimized both SBP and heart rate, both cardiovascular parameters positively correlated with adrenal sympathetic activity. The recovery of gastrointestinal motility and normal feeding were paralleled by body weight increase. The above mentioned clinical + physiological parameters were paralleled by the normalization of the insulin versus glucagon balance throughout the oral glucose tolerance test [2].

The dramatic therapeutic effect triggered by amantadine supports our postulation that it was provoked by the drug throughout CNS mechanisms. With respect to this, we will summarize some information dealing with this issue. The C1(Ad) medullary and the A5(NA) pontine nuclei are the motor center of adrenal and neural sympathetic branches of the peripheral autonomic system (ANS), respectively [3-8]. Glutamate axons excite the former but not the latter nuclei. However, both nuclei interchange inhibitory axons which act at postsynaptic alpha-2 inhibitory receptors [3-8]. The C1(Ad) nuclei send polysynaptic drives to both pancreatic A-cells (secreting glucagon) and to the adrenal glands (secreting adrenaline) [21]. Conversely, A5(NA) neurons send polysynaptic drives to the lumbar sympathetic neurons which excite sympathetic ganglia (that release NA, preferentially and DA). In addition, insulin released from B-cells crosses the bbb and excites the A5(NA) neurons [3-5,22-25] whereas, glucagon, secreted from A-cells crosses the bbb and excites C1(Ad) nuclei [26-30].

Circulating insulin triggers hypoglycemia and enhance gastrointestinal motility and feeding whereas glucagon provokes hyperglycemia and abrogate gastro-intestinal motility, both factors responsible for anorexia [1,9,19,23,31]. The above CNS + ANS neuroendocrine interaction facilitates the understanding of the dramatic annulment of AN syndrome provoked by a small oral dose of amantadine, a drug that interrupt the CNS C1(Ad) + A-cells (glucagon) crosstalk.

Some additional information should facilitate the understanding of the above issue. We were able to demonstrate that insulin crosses the blood brain barrier and excites the NA neurons responsible for the peripheral neural sympathetic activity [22] our findings were ratified by Fisher *et al.* [25]. Furthermore, we also demonstrated that post-prandial hypoglycemia + hyperinsulinism was provoked by the absolute predominance of this sympathetic branch. Evenmore, we found that neuropharmacological manipulation addressed to attenuate this neural sympathetic predominance was able to normalize this post-prandial hypoglycemia + hyperinsulinism disorder [1,23]. The above findings are now complemented by the results presented in this research study showing that the anorexia nervosa syndrome is located at the opposite "face of the coin", namely, adrenergic hyperactivity + hyperglycemia which may be abrogated throughout an adequate neuropharmacological manipulation addressed to revert this face of the coin.

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