HUMET-R Syrup

Preclinical Studies and Clinical Observations

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HUMET RESEARCHES IN MALE RATS

/OBSERVETION OF THE EFFECT OF HUMET DERIVATIVES ON MALE RAT'S SEXUALITY/

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Confidential

This study differs in some aspects from the short summary /Observation of the effect of Humet-derivatives on male rat's sexuality/. It contains quite new experiments which are not included in the summary.

I wrote this study in logical order and pointed out to those experiments which are much more important than others.

To the readers who have not enough patience, I suggest to read the summary only.

Budapest, November 1994

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INTRODUCTION

A sex-stimulant - aphrodisiac - compound has been the dream of mankind for centuries. Popular aphrodisiacs /opiates, plant extracts/ were used in many parts of the world /1./. The research of aphrodisiacs started with the discovery that brain monoamines /dopamine, serotonine/ play an important role im male's sexuality. Dopaminomimetics like bromocriptine enhance the male's sexuality both with animals and men.

/-/ Deprenyl /Jumex, Movegan/ used in the therapy of Parkinson and Alzheimer disease, proved to be a potent, long-lasting true aphrodisiac in aged sexually sluggish male rats /2/.

METHODS

Generally accepted animal model to search aphrodisiac is the sexually active male rat /3/. Sexually active male rats displayed to the receptive females /which show willingness to copulate/ mounting, intromission and ejaculation /4/. These patterns are easy to recognize.

Sex-stimulant compounds are usually tested in sexually active male rats by decreasing the mating patterns and their latencies/3/.

To test an aphrodisiac we needed males in which sexual activity is inherently low. Following this concept I developed a time-consuming test system in male rats which can be repeated in other laboratories as well /5/. We use

a/ male rats which are sexually inactive /they failed to show any copulatory patterns/,

b/ males which displayed only mounting behavior during a four weeks' mating test,

c/ sexually sluggish males which displayed mounting and intromission without ejaculation during a four weeks' mating test, and

d/ sexually active male rats which displayed full scale of copulatory repertoire, including ejaculation.

Testing procedure: the males were put in ovoid shaped boxes and after 5 min. adaptation time each male received a receptive female. The males' copulatory patterns were registered for 30 minutes. Ovariectomized and hormone treated females were used as partners to the males. The copulatory activity of the males was observed once a week.

Humet-S was received by our laboratory just by chance and was tested then in sexually inactive male rats. All males are of Wistar strain, purchased from LATI, Gödöllö, Hungary.

Materials

During the last two years' period we tested different Humet-S /HS/ samples.

Sample No.1. was received in December 1992. It was a black substance upon an undefined solvent in a dark bottle of altogether 400 ml. According to instruction it was kept at 5 C^{o} and was well shaken before use. The substance was administered in a dose of 1 ml/animal/day. One month later we reduced the dose to 1 ml/animal bidaily. As solvent we used a 5% glucose solution.

Sample No.2. was prepared in January 1993 and received by us in July 1993. It was similar to sample No.1. except that it was in a clear bottle of one liter volume.

Sample No.3. has been prepared in March 1993 and we started to work with it in September 1993.

Sample No.4. was received in September 1993. It was a 300 ml original bottle from the Company Humet, containing a dark solution that had to be shaken strongly before use. It was given in a dose of 0,1 ml/animal or 0,3 ml/animal bidaily, orally, solved in running water.

The different Humet-S samples are indicated in this study as follows:

HS_1 = Humet-S sample one

HS_2 = Humet-S sample two

We also made some preliminary experiments with Humet-R which is a dark solution received from the Company Humet in an original bottle of 300 ml.

1.

Experiments with Humet-S_2 in senescent male rats

/An individual case report/

Three, sexually inexperienced 30 months old /body weight 360-410 g/ males' copulatory behavior was checked with receptive females before the treatment, twice for 120 min. All the three senescent males proved to be sexually inactive.

These males were treated with Humet-S_2 0,25 ml/animal orally, three times a week /on Mondays, Wednesdays and Fridays/ and Their mating behavior was controlled 24 hours after the second treatment. This procedure went on for thirty consecutive weeks. /The treatment was started November 21, 1993/. As shown by Table I, one male out of the three started to mate after the second treatment with Humet-S_2 and it displayed full scale of copulation, including ejaculation, after the fourteenth treatment. This result is quite surprising because the male rat looses his ejaculatory ability at the age of 24 months /9/.

Until now ejaculation could be elicited in more than 24 months old male rats only by continuous treatment with 0,25 mg/kg /-/ deprenyl /Jumex, Movegan/ /9, 13/.

These findings suggest that 0,25 ml/animal Humet-S_2 acts similarly as /-/ deprenyl.

A further Humet-S_2 treatment of 30 weeks caused a dramatic increase of the copulatory performance in this male: 4 - 7 ejaculations were observed.

The other two males did not start to copulate in spite of having received the same treatment. One male /No.2/ died in the 16th week of the treatment /he lived 34 months/.

It is outstanding that the body weight of the two survivor males increased, No.1 male put on 50 grammes.

These results showed that

1. Humet-S_2 exerted a true, <u>long lasting aphrodisiac</u> effect on one out of three senescent males. In other words: Humet-S_2 would be a useful tool to approach the male's individuality /in human male as well/. Shortly why has one male responded to the treatment and why have not the others? This question could arise regarding humans, too.
2. Members which responded to the Humet-S_2 treatment, reacted by an enormous copulatory performance, multiple /4-6/ ejaculations.

Treatment was stopped after 30 weeks and the duration of the aphrodisiac effect was checked weekly. As it appears in <u>Table II</u>, the sexual stimulant effect of Humet-S_2 lasted

for several weeks without any further treatment. During this wash-out period the male has retained its high sexual performance: he ejaculated six-seven times for ten weeks.

This long-lasting aphrodisiac effect is peculiar and unique, all the more so because the sex-stimulant effect of /-/ deprenyl ceased after the stopping of the administration. No such effect could be observed in the event of Humet-S_2.

When we want to caracterize the sex-stimulant effect of Humet-S_2 in male rats, the following conclusions can be drawn:

a/ this effect started with a latency of 5-10 days,

b/ the aphrodisiac effect of Humet-S_2 did not appear with each treated male /in this particular case only with one out of three/.

c/ The individuals with which Humet-S_2 proved to be effective, gave an enormous response /high sexual performance/.

d/ after the stopping of the treatment, the sex-stimulant effect was permanently maintained for several weeks.

Considering these points separately:

a/ the long onset of the Humet-S_2 is quite similar to that which was observed with /-/ deprenyl and and /-/ para-fluoro-deprenyl in male rats' sexual behavior /2, 7/

b + c/ The individual effectiveness of Humet-S_2 /this means that it was not effective in all of the treated males/

is similar to the one observed in the event of old, sexually inactive male rats: three males responded enormously to the /-/ para-fluoro-deprenyl treatment, out of fifteen males /Table III./ /7/.

d/ The permanent effect of Humet-S_2 after stopping the treatment could not be elucidated. Some hormones which are used as contraceptives like estrediol-enantate or norgestrel implants could be effective for extraordinarily long time, i.e. six-seven years. /8/.

According to Knoll's data /9, 13/ there is a close correlation between the male rat's sexual activity and its life-span. Thus, non-copulator males, whose treatment with physiologic solution started in their 24th month of age, lived 142 weeks, while /-/ deprenyl treated rats /0,25 mg/kg s.c. three times a week/ lived still longer /187 weeks/.

At present there is no other drug which would be able to achieve this effect.

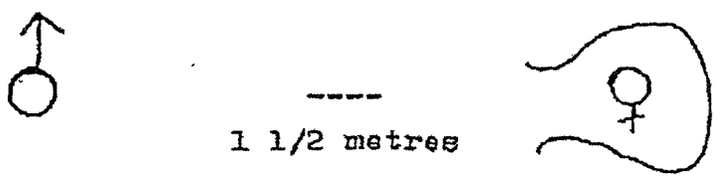
The males treated with Humet-S_2 in a dose of 0,25 ml per animal are still alive, they are 41 months old at the time of closing this paper. Thus it seems that Humet-S_2 is able to extend the life-span in male rats. It is also interesting that only one senescent male copulated while the others did not but they are still alive just like the copulator.

In the following I will describe a new series of experiments with Humet-S_2 in these two senescent male rats: it elicited female-seeking behavior which perviously could be achieved only through a special "sex-training" in young male rats /10,11/.

The essence of the above mentioned training is that female rats are thrown quickly and one by one to the male into the copulatory box. When the male has displayed three mountings or one intromission, he receives a new female. Thus a male meets at least 20-30 females during a 30 min. test period.

When we continue this procedure for 40-60 days, the male seeks the female in a big open field /length: 2 metres or more/, too and begins to copulate with her. This female seeking behavior in males can be elicited permantly: he seeks the female again, even immediately after the ejaculation, and what is more after castration as well.

Humet-S_2 treated senescent males permanently displayed female seeking behavior.



position of the male

female in the box

In Protocol one I reported the female seeking behavior of No.1. and No.3. senescent males. We registered the time when the male reached the box containing the female, the time when he entered the box and his copulatory activity towards the female. Four consecutive seeking tests with the two senescent male rats are presented in Protocol one. After ejaculation the males have immediately restarted.

Male No.1. age 40 months, body weight: 450 gms.
Male No.3. age 40 months, body weight: 440 gms.

The senescent male No.1. has continuously displayed partner-seeking behavior, he ejaculated during all the four seeking tests just as we observed this previously with young males which underwent the special "sex-training". The senescent male No.1. shows this partner-seeking behavior without this "sex-training". No.3. senescent male displayed the same partner-seeking behavior as young, castrated seeker males. As an explanation for this it is also possible that Humet-S_2 has a specific central nervous system stimulant effect.

Anyway, during my thirty years of experimental practice I never have experienced this phenomenon so far.

I wish to stress again that up till now "female-seeking" behavior of male rats could not be developed without a long lasting "sex-training", nor could it be elicited by drugs acting on the cetral nervous system /amphetamines, /-/ deprenyl/.

It seems that Humet-S is the first drug mixture which can elicit female seeking behavior, mainly in senescent males. It is a fact that one male /No. 1/ which was 30 months old and was sexually inactive, after having received 0,25 ml/animal Humet-S_2 treatment became sexually active, and displayed an enormous sexual performance which continued also after the stopping of the treatment.

This male displayed female-seeking behavior with repeated copulation /see Protocol one/ at the age of 41 months - which age is not reached by the majority of rats - is a unique observation in my more than 30 years of experimental work.

The effectiveness of Humet-S_2 in inducing partner seeking behavior in male rat without copulation suggests that there is a special central nervous system stimulating effect of Humet-S_2.

These results suggest that a new concept of aging /brain/ should be elaborated. /See Future, Paragraph 3 on Page 16/.

One may ask what is the importance of a phenomenon which could be observed only with one male? My answer is that if I can teach a rat to play the piano then it is possible that all rats are able to play the piano but we have to find the particular way of teaching each individual. Those who are familiar with neurophysiology will know the name of Gnatt /12/ who was able to demonstrate in his famous dog Nick the whole neurophysiology and neuropathology.

2.

Experiments with Humet-S_1 in aged, sexually inactive male rats

Six sexually inactive ten months old male rats /body weight 420-510 g/ were started to be treated with Humet-S_1 1 ml per animal, orally, every other day. The copulatory activity of the males was checked 24 hours after the fifth treatment and it was followed for fifteen consecutive weeks. Then the treatment was stopped and the males' copulatory performance continued in a period of altogether 62 weeks.

Two males out of six displayed high copulatory performance with multiple ejaculation /2-4/ consistently during a 30 min. testing period. This finding also supports the view that Humet-S_1 acts as an individual aphrodisiac /see Point 1/ like /-/ para-fluoro-deprenyl /Table IV/.

Table IV shows the copulatory performances before and after the Humet-S_1 treatment. The administration of Humet-S_1 was stopped after 15 weeks. One male became sexually active in the 29th week of the drug free period. An enormous long lasting aphrodisiac effect was observed also in the wash-out period: fifteen weeks /16-30/. Moreover it seems that this effect was much more pronounced in the second part of the was-out period/31-46 weeks/. Full copulatory repertoire could be detected still in the 62th week of the observation.

As I mentioned in Point 1, there is not available any drug acting for so long time as Humet-S_1. From physiological point of view it is possible that there is a continuous inhibition in the brain which can be irreversibly destroyed by Humet-S_1. Anyway, the long lasting aphrodisiac effect of Humet-S_1 served as a useful tool to control mechanisms of the sexual behavior. Each of the treated males is still alive at 25 months of age. As shown on Table V, also an increase of the body weight of the treated animals was registered in the 30th week of the observation.

In addition to the previous data it is to be mentioned that a single dose of 3 ml Humet-S per animal could be effective for 30 weeks /Table VI/.

These results also suggest a similarity between Humet-S and our results with /-/deprenyl /6/.

3.

Experiences with a new Humet-S sample /HS_4/

Also this sample was tested in sexually inactive old male rats which were ten months old at the beginning of the experiment. Humet-S_4 solution was given orally, bidaily in a dose of 0,1 ml and 0,25 ml every other day and behavorial tests were carried out also every other day.

For the sake of comparison we used a solvent /running water/ group. Each group consisted of 10 males. The data are shown by Table VII.

4.

Preliminary experiments with Humet-R

Eight sexually inactive male rats were treated in a dose of 1 ml/animal Humet-R daily. The males were ten months old and their body weight varied between 420 and 550 gms at the beginning of the experiment. After the control tests, both treatment and copulatory tests were carried out bidaily. Table VIII shows the results. The body weight of the treated males /with the exception of male No.1/ did not change significantly. /Table IX/

This sample proved to be effective in stimulating the copulatory activity in sexually inactive males, in the same manner as the previous Humet samples. All the eight males became sexually active, but the aphrodisiac effect was developed with longer latencies /1, 3, 4, 4, 4, 11, 13, 17 weeks resp./.

Solvent treated males displayed a weaker copulatory performance with one and two weeks' latency.

Table X summarizes the data of this study. Ten males out of thirty became sexually active as a result of the Humet-S treatment. /Table X. Items 2, 3, 4/. Though all Humet-R treated males responded to the treatment /Table X, Item No.5/ it seems that the aphrodisiac effect of Humet-S is much more pronounced /Table X Items 3 and 5/. According to my opinion there are differences between the Humet-S samples.

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CONCLUSIONS

Humet-S exerts a strong aphrodisiac effect on old, sexually inactive male rats. This effect can be caracterized as follows:

1. The sex stimulant effect does not start immediately, its development has more or less latency. This varies between five /Humet-S_1/ and fourteen days /Humet-S_2/. Sometimes still longer time is necessary to achieve this effect: twenty-one or thirty days /Humet-S_4/.
2. The above mentioned effect was observed when the males were treated every other day, orally in a dose of 0,1 ml - - 0,3 ml - 0,25 ml or 1 ml/animal.
3. Humet-S treatment was not effective in each of the treated males, only in some members of the treated group.
4. Males which responded to the treatment, displayed an enormously high sexual performance: in aged group 4-5 ejaculations, moreover in one senescent male /30 months of age/ six-seven ejaculations could be observed.
5. It is remarkable that we induced high sexual performance with Humet-S in aged males, in contrast to our present knowledge according to which male rats over 24 months of age loose their ejaculatory ability /9, 13/.

6. The aphrodisiac effect of Humet-S lasts for a long time after stopping the treatment.

7. It is striking that Humet-S interferes with the aging process. It extended several individuals' life span. /We have two Humet-S treated male rats which are 41 months old./

8. Humet-S induced in two senescent males a female-seeking behavior which could not be induced by any other known central nervous system stimulant drug. Such behavior was present in males whih underwent a special sex training /11/.

9. The effect which was observed with Humet-S strongly resembles to our experiments with /-/ deprenyl and /-/ para-fluoro-deprenyl in respect of its ability to extend the life-time in male rats.

10. Preliminary experiments with Humet-R showed that it is effective in the whole treated group but with a longer latency than Humet-S.

FUTURE

Why is Humet-S interesting?

1. It possesses a sex-stimulant effect on a certain proportion of male rats.

2. It interferes with the aging process as well.

3. According to Knoll's concept of aging the striatal dopamine decreases gradually during the aging process, thus the consequences of the decreased dopamine content could be antagonized by /-/ deprenyl intake. American authors reject this suggestion but it is possible that the aging could be counteracted with continuous Humet-S intake.

Surely rats' experiments are difficult to be extrapolated into man but with a non-toxic mixture like Humet-S we can jump over the big distance which exists between rats and humans.

PROTOCOL NO. ONE

on the female seeking behavior of two,
Humet-S_2 treated male rats

Female Seeking Test No.	Male Rat No. 1				Male Rat No. 2			
	1.	2.	3.	4.	1.	2.	3.	4.
He reached the box	45"	15"	55"	45"	15"	50"	30"	12'10"
He entered the box	50"	2'00"	1'30"	45"	30"	55"	50"	12'15"
Started to copulate	1'40"	5'00"	6'00"	6'50"	-	-	-	-
Number of Mountings	12	10	10	5	0	0	0	0
Number of Intromissions	10	4	6	3	0	0	0	0
Ejaculation time	11'50"	8'00"	10'45"	10'05	0	0	0	0

TABLE I

Mounting /M/, Intromission /I/, Ejaculation /E/ and Body Weight /bw./ data of three Humet-S_2 treated male rats during sixteen 120 minutes' mating tests

Week No. of the test	Number of the received Humet-S_2 treatments	Male No.1				Male No.2			Male No.3				
		M	I	E	bw. gms	M	I	E	M	I	E	bw. gms	
1.	-	0	0	0		0	0	0	0	0	0		
2.	-	0	0	0		0	0	0	0	0	0		
3.	2	67	0	0	/400/	0	0	0	0	0	0	/410/	
4.	5	1	0	0		0	0	0	0	0	0		
5.	11	4	0	0		0	0	0	0	0	0		
6.	14	101	22	1		0	0	0	0	0	0		
8.	17	88	24	4		0	0	0	0	0	0		
10.	23	57	35	6		0	0	0	0	0	0		
12.	29	25	37	6		0	0	0	0	0	0		
14.	35	76	42	5		0	0	0	0	0	0		
16.	44	25	21	5		0	0	0 +	0	0	0		+ Male No.2 died on 06.03.1994.
21.	59	72	32	5					0	0	0		
23.	65	58	44	6					0	0	0		
25.	71	49	27	4					0	0	0		
27.	77	57	42	7					0	0	0		
30.	83	27	13	2	/450/				0	0	0	/420/	

T A B L E II

Sexual stimulant effect of Humet-S_2 in male rat No.1

Number of weeks after the treatment	M*	I*	E*	Age in months	Body weight gms
1	37	32	7	37	440
2	36	30	6		
3	60	43	7		
4	57	43	7		
5	9	2	0		
6	25	0	0		
7	98	4	1		
8	81	4	1		
9	32	29	7		
10	95	41	6	39	440

*Remarks: M = Number of Mountings

I = Number of Intromissions

E = Number of Ejaculations

during a 120 minutes' test period.

T A B L E III

Sexual activity of three aged male rats treated with para-fluoro-deprenyl in a dose of 0,25 mg/kg body weight for twenty-five months.

/Test duration: 120 minutes/

	Mountings	Intromissions	Ejaculations
Male No. 1	32	17	6
Male No. 2	9	12	4
Male No. 3	32	15	1

T A B L E IV

Total number of mountings, intromissions and ejaculations during a 62 weeks' observation period with 6 sexually inactive male rats. Humet-S_1 treatment /1 ml/animal/ began after the fourth test bidaily and lasted for 15 weeks.

	Mountings /M/	Intromissions /I/	Ejaculations /E/
Period:			
1 - 4 weeks	0	0	0
5 - 15 weeks	459	401	75
16 - 30 weeks	657	518	95
31 - 46 weeks	737	896	136
47 - 62 weeks	500	499	55

Remark: each test lasted 30 minutes.

T A B L E V

The body weight /in grammes/ of six sexually inactive male rats at the beginning /0/ of a 15 weeks' Humet-S_1 treatment /1 ml/animal bidaily, orally/, in the fifteenth week of the treatment /15/ and in the thirtieth week /30/ after the beginning of the treatment

Humet-S_1 treated Male No:	0	15	30
	weeks after starting the treatment		
1.	500 /gms/	490	520
2.	440	380	470
3.	510	450	530
4.	410	390	415
5.	500	370	500
6.	425	400	430

T A B L E VI

Treatment	Total number of Mountings /M/ Intromissions /I/ and Ejaculations /E/					
	1-15 weeks			16-30 weeks		
	M	I	E	M	I	E
Single administration of Humet-S_2 3 ml/animal orally /Sexually active male rats N = 6/	669	459	60	1238	956	110
Repeated administration of Humet-S_1 1 ml/animal orally bidaily for 15 weeks /Sexually inactive male rats N = 6	459	401	75	657	518	95
Repeated administration of Humet-S_2 0,25 ml/animal orally bidaily for 30 weeks /One sexually inactive male rat	740	308	38	680	374	51

T A B L E VII

Effect of a new Humet-S sample /HS_4/ in sexually inactive male rats, administered orally every other day in a dose of 0,1 ml and/or 0,25 ml per animal, in comparison to solvent treated males. /Ten males in each group/.

Dose of the treatment	No. of males out of 10 which responded	Time in weeks when they	Total number of mountings /M/, intromissions /I/ and ejaculations /E/ before, during and/or after the treatment								
			M	I	E	M	I	E	M	I	E
Humet-S_4 0,1 ml per animal	3	2,3,4 resp.	0	0	0	1-4 weeks: 130	53	7			
Humet-S_4 0,25 ml per animal	3	2,4,6 resp.	0	0	0	1-15 weeks: 206	133	20	16-30 weeks: 120	56	14
Solvent	2	3,4 resp.	0	0	0	83	34	7	0	0	0

T A B L E VIII

Total number of mountings /M/ intromissions /I/ and ejaculations /E/ observed in eight sexually inactive male rats during a 35 weeks' treatment with 1 ml/animal Humet-R orally, daily.

	Mountings /M/	Intromissions /I/	Ejaculations /E/
Before the treatment	0	0	0
From the 1st to 15th week of the treatment	408	253	19
Between the 16th and 30th week	237	133	21
Between the 31st and 35th week	1	0	0

Remark: two males died /one in the 15th and the other in the 20th week of the treatment/.

T A B L E IX

The body weight of the Humet-R treated males before and during the 35 weeks' treatment /orally 1 ml/animal daily/

/Weight data in grammes/

Male No.	Before treatment	In the 15th week	In the 30th week
1	420	450	320
2	460	460	440
3	435	460	-
4	550	545	555
5	520	-	-
6	510	505	520
7	505	560	535
8	490	505	515

T A B L E X

Sexual Activity /Mountings = M, Intromissions = I and Ejaculations /E/ of Male Rats resulting from orally administered Humet derivatives /Humet-R daily, Humet-S every other day/.

Item	Treatment	Proportion of males responded/ /tested	1-4. weeks before the treatment			1 - 15. weeks during and/or after the treatment			16 - 30. weeks during and/or after the treatment			Latency in males which responded /weeks/
			M	I	E	M	I	E	M	I	E	
1.	Solvent	2/10	0	0	0	83	34	7	0	0	0	3,4 resp.
2.	Humet-S_4 0,1 ml	3/10	0	0	0	130	53	7	0	0	0	2,3,4 resp.
	0,25 ml	3/10	0	0	0	206	133	20	120	56	14	2,4,6 resp.
3.	Humet-S_1 1 ml	3/6	0	0	0	459	401	75	657	518	95	1,1,16 resp.
4.	Humet-S_2 0,25 ml	1/3	0	0	0	740	308	38	680	374	51	2
5.	Humet-R 1 ml	8/8	0	0	0	408	253	19	237	133	21	1,3,4,4, 4,11,13, 17 resp.

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