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Interrelation between histamine and serotonin, dopamine, GABA, IGF-1 in a growth hormone (GH) deficient group under rh-GH replacement therapy

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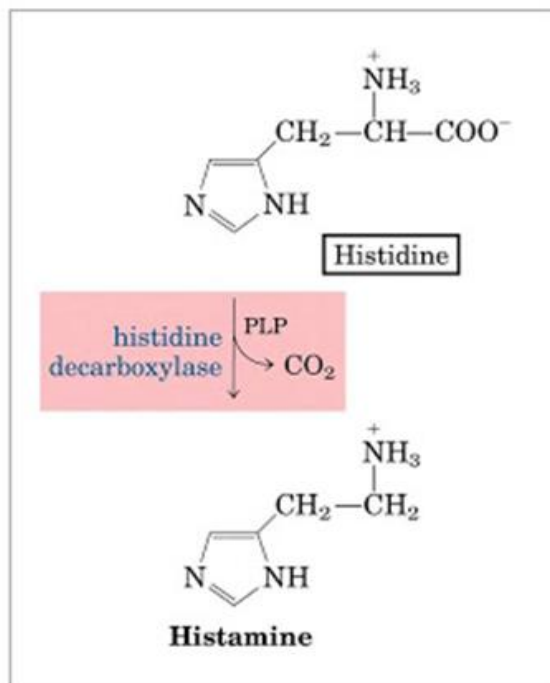
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Graphical Abstract



HIGH HIST →
5-HT
DA
GABA
IGF1

LOW HIST →
5-HT
DA
GABA
IGF1



Abstract:

Aim: To evaluate relationship between histamine (HIST), serotonin (5-HT), dopamine (DA), gamma-amino-butyric acid (GABA) and IGF-1 in 20 GH deficient boys.

Research design and methods: This study included 20 boys (5-14 years) with GH deficit clinically established and a 10 matched normal group with no endocrine dysfunction. All of GH deficient patients underwent GH replacement therapy. In 2017, all subjects were tested by analytical methods for blood: HIST, GABA, DA, 5-HT, IGF-1.

Results: We divided this study group into a low HIST lot 1 (10 subjects): HIST median: 3.48 nM/L and a high HIST lot 2 (10 subjects): HIST median: 11 nM/L. Median parameters in lot 1 vs. lot 2 was: 5-HT: 212.5 vs. 370 ng/mL, DA: 30 vs. 45 pg/mL, GABA: 30 vs. 56.5 ng/mL, IGF-1: 373.5 vs. 200 ng/mL. Median values in normal subjects were as it follows: HIST: 5.55 nM/L; 5-HT: 235.5 ng/mL; DA: 31.5 pg/mL; GABA: 81 ng/mL. T-Test revealed a statistical significance between HIST in lot 1 vs. lot 2 ($P < 0.001$), HIST in lot 1 vs. normal group ($P < 0.01$) or HIST in lot 2 vs. normal group ($P < 0.01$). We can also underline a statistical significance between 5-HT in lot 1 vs. lot 2 ($P < 0.05$) or in lot 2 vs. normal group ($P = 0.01$).

Conclusion: Our study underlined a HIST/5-HT positive relationship in low HIST group vs. a negative relationship HIST/5-HT in high HIST group: with small IGF-1 increments under r-GH therapy.

Keywords: *histamine; serotonin; dopamine; gamma-amino-butyric acid; GH-deficiency*



Introduction

- Both amine and aminoacid neurotransmitters are implied in the control of GH release, either stimulating or inhibiting hormone release
- This dual effect results from an action of the same molecule at both GHRH and somatostatin-secreting neurons
- As a result of GH secretion, both GH itself and the GH dependent insulin-like growth factor (IGF-I) exert an inhibitory feedback through hypothalamic or pituitary sites or both
- GHRH and somatostatin release are controlled by a complex neuronal network, in which α -adrenergic, dopaminergic and serotonergic signals stimulate GH secretion



- Although neurotransmitters cannot readily enter the brain, basic and clinical research has established the relationship between central nervous system (CNS) and peripheral nervous system (PNS) neurotransmitter activities
- It is possible to obtain some information regarding CNS function through the measurement of circulating neurotransmitters
- Among neurotransmitters: histamine (HIST) dopamine (DA), serotonin (5-HT), epinephrine / norepinephrine, and also gamma-aminobutyric acid (GABA) are involved in the GH control release
- The stimulatory or inhibitory influences on GH secretion of brain neurotransmitters studied so far, as derived: HIST action not ascertained, DA in humans: stimulation or inhibition; 5HT: stimulation or inhibition action still questionable; GABA: stimulation



- **HIST is synthesized by histidine decarboxylase (HDC; EC 4.1.1.22) from L-histidine in different cellular compartments (mast cells, basophils, glial cells, endothelial cells, neurons)**
- **HIST is metabolized (in tele-methylhistamine) by histamine N-methyltransferase (HNMT) which inactivates it**
- **Histamine regulates neurotransmitter release in the central and peripheral nervous systems through H₃ presynaptic receptors**
- **Histamine H₃ receptor found on central nervous system and to a lesser extent in peripheral nervous system influences release of HIST, serotonin**
- **Histamine appears to be involved in stimulated GH release**
- **The aim of this study was to underline the relationship between HIST, 5-HT, DA, GABA, IGF1 in GH-deficient children**



Results and discussion

- **Our study (2017) enrolled 20 boys aged: 5-14 years clinically identified as GH-deficient after a detailed anamnesis, anthropometric measurements and different dynamic tests**
- **All of them underwent over time replacement rh-GH therapy in established doses**
- **In 2017 all these patients were investigated for plasma HIST,GABA,DA and serum 5-HT,IGF-1**
- **A normal group included 10 boys aged:7-16 years with no endocrine dysfunction**



- All subjects collected in the morning at 9 am(after an overnight fasting, free of drugs) 2 samples of plasma (into EDTA vacutainers) and a sample of total blood**
- After centrifugation, plasma and serum samples were aliquoted and stored at -20°C until assayed**
- Plasma HIST, GABA, DA and serum 5-HT were evaluated by research Elisa methods**
- Serum IGF-1 was evaluated by a chemiluminescent method**
- Statistical processing of data was done using MedCalc Software version 14.8.1**



- We divided this 20 patients group into a low HIST lot 1(10 subjects): median:3.48nM/L and a high HIST lot2(10subjects) median:11nM/L by comparison with a normal HIST lot(lot N:10subjects) median:5.55nM/L
- Range and medians for all 5 tested parameters are inserted in *Table1*
- T-test showed a statistical significant difference between HIST in lot 1vs. Lot2 ($P<0.001$) or HIST in lot 1 vs. normal lot(lot N)($P<0.01$) or in lot 2 vs. lot N($P<0.01$)
- We can also underline a statistical significance between 5-HT in lot 1 vs.lot 2 ($P <0.05$) or in lot 2 vs. lot N ($P=0.01$)
- Comparison between medians in all 3 groups are showed in *Fig.1*



- **DA, GABA, IGF-1 are not different statistically between lot 1 vs. 2 or vs. lot N**
- **Multiple regression coefficients between different parameters were established (*Table 2*)**
- **A high correlation was established between HIST/5-HT in Lot 1 ($R=0.87$) and a negative correlation in Lot 2 ($R=-0.48$)**
- **HIST/DA are high correlated in Lot 1 ($R=0.69$) or in Lot 2 ($R=0.63$)**
- **HIST/GABA are well correlated in Lot 1 ($R=0.61$) or in Lot N ($R=0.51$)**
- **5-HT/DA are high correlated in Lot 1 ($R=0.78$) and a negative correlation was established in Lot 2 ($R=-0.59$)**



- High positive correlations between 5-HT/GABA were established both in Lot 1: $R=0.78$ and in Lot 2: $R=0.63$
- 5-HT was correlated with IGF-1 in Lot 1: $R=0.54$
- A negative correlation was established between DA and IGF1 in Lot 2: $R=-0.62$
- Deficient GH children with low HIST(lot1) showed high positive correlations between HIST:5-HT :*Linear regression equation:*
 $y = 25,133x + 141,94$
- Deficient GH children with high HIST(lot2) showed negative correlation between HIST:5-HT :*Linear regression equation:*
 $y = -7,1602x + 436,31$



- **There was no clinical evidence that children GH-deficient selected for this study would have any dysfunction related to histamine metabolism**
- **Following release from the neuron, extracellular HIST levels are regulated by two processes namely: HIST metabolism (degradation to tele-methylhistamine) and receptor autoregulation**
- **Increased HIST synthesis could result in increased histaminergic neuronal activity due to increased HIST release**
- **H₃HIST receptors continuous exposure to high HIST concentration may lead to decreased number of receptor sites consistent with a selective down-regulation of these receptors**
- **We could suppose a down-regulation of H₃HIST receptors trying to explain high HIST level in our selected group of GH-deficient children**



- HIST stimulates the release of serotonin and could be an explanation for 5-HT significant increase in this patients
- On the other hand it could be an influence of H₃HIST receptor by feedback inhibition of HIST synthesis and release and so, a possible explanation for low HIST level in our selected group of GH-deficient children
- In recent studies was related a decrease of serotonin as a consequence of the the great expression of H₃HIST receptor
- So, in low HIST GH-deficient children we could explain a significant decrease of 5-HT compared to 5-HT values in high HIST Lot1



CONCLUSIONS

- **Our biochemical study pointed out the role of histamine in a group of GH-deficient children seemingly unrelated with GH-deficit but correlated with serotonin**
- **We suggest this marker investigation on a larger group of GH-deficient children**
- **We believe it deserves the effort to investigate the involvement of the histamine H₃HIST receptor in this pathology**



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Table 1- Range, median of all 5 parameters in manic boys vs control subjects

Subjects number	HIST nM/L Range/ Median	5-HT ng/mL Range/ Median	DA pg/mL Range/ Median	GABA ng/mL Range/ Median	IGF-1 ng/mL Range/ Median
LOT1 10 boys	1- 6.29 3.48	165 - 330 212.5	18 - 67 30	19-105 48	76 - 818 334
LOT2 10 boys	8.97-28.4 11	158 - 479 370	12 - 57 45	36-70 56,5	85 - 445 200
LOT N 10 normals	4.14- 6.86 5.55	111 - 324 235,5	27- 71 31,5	41-95 58.5	–
T-TEST LOT1vs.LOT2	P<0.001	P<0.05	NS	NS	NS
T-TEST LOT1vs.LOT N	P<0.01	NS	NS	NS	–
T-TEST LOT2 vs.LOTN	P<0.01	P=0.01	NS	NS	–



Table 2 - Pearson coefficients between different neurotransmitters in all studied groups

Pearson coefficient R	HIST/ 5HT	HIST/ DA	HIST/ GABA	HIST/ IGF-1	5-HT/ DA	5-HT/ GABA	5-HT/ IGF-1	DA/ GABA	DA/ IGF-1
LOT 1	0.87	0.69	0.61	0.44	0.78	0.78	0.54	0.36	0.18
LOT 2	-0.48	0.63	0.35	0.34	-0.59	0.63	0.34	0.45	-0.62
LOT N	0.46	0.19	0.51	–	0.21	0.45	–	-0.32	–



FIG.1- Comparison of the medians for all 5 parameters evaluated in all studied groups

