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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Graphical Abstract
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: 11nM/L. Median parameters in lot 1 vs. lot 2 was: 5-HT: 212.5 vs. 370ng/mL, DA: 30 vs. 45pg/ml, GABA: 30 vs. 56.5ng/mL, IGF-1: 373.5 vs. 200ng/mL. Median values in normal subjects were as it follows: HIST: 5.55nM/L; 5-HT: 235.5ng/mL; DA: 31.5pg/mL; GABA: 81ng/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
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 lot 2 (10 subjects) median: 11nM/L by comparison with a normal HIST lot (lot N: 10 subjects) 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 1 vs. 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 nanic boys vs control subjects**

<table>
<thead>
<tr>
<th>Subjects number</th>
<th>HIST nM/L Range/ Median</th>
<th>5-HT ng/mL Range/ Median</th>
<th>DA pg/mL Range/ Median</th>
<th>GABA ng/mL Range/ Median</th>
<th>IGF-1 ng/mL Range/ Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT1 10 boys</td>
<td>1- 6.29 3.48</td>
<td>165 - 330 212.5</td>
<td>18 - 67 30</td>
<td>19-105 48</td>
<td>76 - 818 334</td>
</tr>
<tr>
<td>LOT2 10 boys</td>
<td>8.97-28.4 11</td>
<td>158 - 479 370</td>
<td>12 - 57 45</td>
<td>36-70 56,5</td>
<td>85 - 445 200</td>
</tr>
<tr>
<td>LOT N 10 normals</td>
<td>4.14- 6.86 5.55</td>
<td>111 - 324 235,5</td>
<td>27- 71 31,5</td>
<td>41-95 58.5</td>
<td>_</td>
</tr>
<tr>
<td>T-TEST LOT1vs.LOT2</td>
<td>P&lt;0.001</td>
<td>P&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>T-TEST LOT1vs.LOT N</td>
<td>P&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>_</td>
</tr>
<tr>
<td>T-TEST LOT2 vs.LOTN</td>
<td>P&lt;0.01</td>
<td>P=0.01</td>
<td>NS</td>
<td>NS</td>
<td>_</td>
</tr>
</tbody>
</table>
Table 2 - Pearson coefficients between different neurotransmitters in all studied groups

<table>
<thead>
<tr>
<th>Pearson coefficient R</th>
<th>HIST/5HT</th>
<th>HIST/DA</th>
<th>HIST/GABA</th>
<th>HIST/IGF-1</th>
<th>5-HT/DA</th>
<th>5-HT/GABA</th>
<th>5-HT/IGF-1</th>
<th>DA/GABA</th>
<th>DA/IGF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT 1</td>
<td>0.87</td>
<td>0.69</td>
<td>0.61</td>
<td>0.44</td>
<td>0.78</td>
<td>0.78</td>
<td>0.54</td>
<td>0.36</td>
<td>0.18</td>
</tr>
<tr>
<td>LOT 2</td>
<td>-0.48</td>
<td>0.63</td>
<td>0.35</td>
<td>0.34</td>
<td>-0.59</td>
<td>0.63</td>
<td>0.34</td>
<td>0.45</td>
<td>-0.62</td>
</tr>
<tr>
<td>LOT N</td>
<td>0.46</td>
<td>0.19</td>
<td>0.51</td>
<td>_</td>
<td>0.21</td>
<td>0.45</td>
<td>_</td>
<td>-0.32</td>
<td>_</td>
</tr>
</tbody>
</table>
FIG. 1- Comparison of the medians for all 5 parameters evaluated in all studied groups