Article

Changes in DOPAC, 3-MT, DOPAC/DA, HVA/DA, 3-MT/DA in the Hippocampus After Simulated Septoplasty and Maxillary Sinusotomy

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Abstract. *Objective:* to evaluate changes in DOPAC, 3-MT, DOPAC/DA, HVA/DA, 3-MT/DA in the hippocampus after simulation of septoplasty and maxillofacial surgery in rats.
Materials and methods. Simulation of operations was carried out on male Wistar rats under general anesthesia with Zoletil 100 solution. In group 1, septoplasty (n=10) was simulated by the standard method by zigzag scarification of the nasal mucosa. In group 2 (n=10), dental implantation with a titanium implant was performed after the implant bed was formed using drill. In group 3 (n=10), only implant bed was made in the alveolar ridge of the upper jaw without subsequent manipulations. In group 4, 10 rats underwent sinus lifting with bone chips with immediate implantation of a titanium implant. In group 5 (n=10)– with the help of a micro drill through a pre-formed implant bed in the alveolar ridge of the upper jaw, a maxillary sinusotomy was performed with damage to the mucous membrane of the ipsilateral maxillary sinus. Liquid chromatography with electrochemical detection was used to determine the concentration of dopamine (DA), homovanilic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), 3- methoxytiramine (3-MT) in the hippocampal formation. DOPAC/DA, HVA/DA, 3-MT/DA were also determined.
Results. The concentration of dopamine in the hippocampus, compared with the control, was significantly higher in group 5 and lower in group 4. The HVA concentration was significantly higher in group 2, group 5 ($p<0.01$) and group 1 ($p<0.05$). An intergroup comparison determined that the concentration of HVA was significantly higher in group 2, compared with the rest of the experimental groups ($p<0.001$). In groups 1, 3 and 4, this indicator was significantly lower compared to group 5 ($p<0.01$). The DOPAC level was significantly higher ($p<0.01$) compared to the control data. The concentration of 3-MT was significantly higher in groups 4 and 5 ($p<0.001$), as well as in group 1 ($p<0.05$) and in group 3 ($p<0.01$).
Conclusion. After simulating sinus lifting with immediate implantation and dental implantation complicated by maxillary sinusotomy, there is an increase in the concentration of dopamine metabolites 3-MT, HVA and DOPAC, but at the same time a decrease in dopaminergic activity of the hippocampal formation, compared with simulation of septoplasty and simple damage to the alveolar ridge of the upper jaw. Such changes are markers of disruption of adaptation processes after surgery in the head and neck.

Keywords: septoplasty, hippocampus, dentate gyrus, dopamine, homovanilic acid, DOPAC, 3- MT, DOPAC/DA, HVA/DA, 3-MT/DA.

1. Introduction

Many diseases of the nasal cavity and maxillofacial region require surgical treatment [1-6]: curvature of the nasal septum [2,7], dental implantation [8], sinus lifting [9].

It is known that in addition to the hypothalamic-pituitary-adrenal axis, the hoppocampal formation, including the hippocampus and the dentate gyrus, also participates in the stress response of the body [10]. Previously, it was found that after surgical simulation in the nasal cavity, the body responds with changes in heart rate variability [11], a violation of the normal function of the autonomic nervous system [12], a massive release of gluco- and mineralocorticoids into the blood plasma in the first 2-5 days after surgery [13], as well as changes in the cytoarchitectonics of the pyramidal layer of the hippocampal formation [14]. The hippocampal formation reacts very subtly to external and internal stress factors, for example, monoaminergic systems [15]. Thus, its noradrenergic, serotonergic and dopaminergic systems are particularly sensitive to such effects [16].

Previously, there have been no studies aimed at studying the monaminergic systems of the hippocampus, in particular, dopaminergic, after simulation of surgical interventions in the nasal cavity, upper jaw and paranasal sinuses.

In this regard, the aim of this study was to study the response of the dopaminergic system of the hippocampus in the early postoperative period in response to surgical interventions in the maxillofacial region in rats.

2. Materials and Methods

2.1. Simulation of operations.

The study used male rats of the Wistar line weighing 210-280 g. Surgical interventions in all groups were performed under general anesthesia with the introduction of a solution of Zoletil 100 into the tail vein. In the first group, septoplasty (n=10) was simulated by the standard method by zigzag scarification of the nasal mucosa according to the standard method [13, 17]. In the second group (n=10), dental implantation with a titanium implant was performed after the implant bed was formed using drill (Fig. 1a). In the third group (n=10), only implant bed was made in the alveolar ridge of the upper jaw without subsequent manipulations (Fig. 1b). This group was a comparison group for groups with dental surgical interventions. In the fourth group, 10 rats underwent sinus lifting with bone chips with immediate implantation of a titanium implant (Fig. 1b). In the fifth group (n=10), with the help of a micro drill through a pre–formed implant bed in the alveolar ridge of the upper jaw, maxillary sinus was performed with damage to the mucous membrane of the ipsilateral maxillary sinus (Fig. 1g)

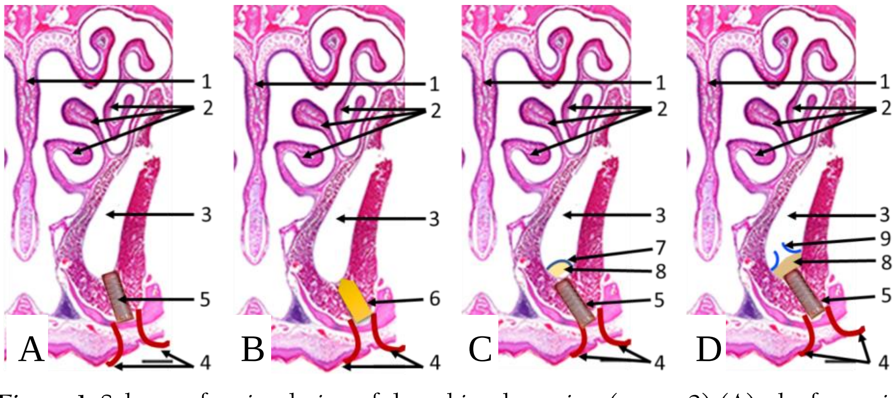

Figure 1. Schemes for simulation of dental implantation (group 2) (A), the formation of implant bed in the alveolar ridge of the upper jaw (group 3) (B), sinus lifting with immediate implantation (group 4) (C) and sinus lifting complicated by maxillary sinusotomy (group 5) (D). Note: 1 – nasal septum; 2 – nasal concha; 3 – maxillary sinus; 4 – mucous-periosteal leaves after incision; 5 – implant; 6 – implant bed; 7 – mucous membrane of the paranasal sinus; 8 – bone chips; 9 – damaged mucous membrane of the paranasal sinus.

2.2. High-performance liquid chromatography with electrochemical detection (HPLC ED).

On the 4th postoperative day after each experimental group animals were euthanized with toxic doses of Zoletil 100 solution, after which the animals underwent guillotining and trepanation of the skull and brain extraction without prior infusion. The obtained samples were homogenized in 1.0 ml of 0.1 n HClO4. with the addition of 250 picomol/ml of the internal standard (3,4-digtdroxybenzyl amine, DHBA) DGBA. The samples were centrifuged at 12,000 g for 10 min on an EPPENDORF 5415R refrigerated centrifuge. The filler liquid in the amount of 20 ml was applied to the analytical column by direct injection and through the Reodyne7125 injector. Dopamine (DA), homovanilic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxytiramine (3-MT, 3-methoxy-4-hydroxyphenethylamine) were separated on a reverse-phase column ReproSil-Pur, ODS-3, 4x100 mm, particle size 3 microns (Dr.Majsch GMBH) using as a mobile phase a citrate-phosphate buffer pH 3.85 containing 0.03 M Na2PO4*2H2O, 0.025M anhydrous citric acid, 0.6 mM sodium octansulfonate, 0.02 mM EDTA and 8% acetonitrile. The determination of monoamines and their metabolites was carried out on a glass-carbon electrode at a potential of +0.85 V against the Ad/AgCl of the reference electrode. The flow rate of the mobile phase was 1.0 ml/min (on an isocratic chromatograph using a GILSON-307 pump (France) and an LC-4B electrochemical detector (Bioanalytical sys., USA).

The samples were registered using the MULTICHROME 1.5 (AMPERSAND) hardware and software complex. All reagents used for the analysis were of a high degree of purity: O.S.C., H.C. or Analytical Grade. To calibrate the chromatograph, mixtures of working standards of the substances to be determined at a concentration of 500 picomol/ml were used.

The concentrations of monoamines in the experimental samples were calculated by the "internal standard" method, based on the ratio of the peak area in the standard mixture and in the sample. All reagents used for the analysis were of a high degree of purity: O.S.C. or analytical grade. The mobile phase was filtered under vacuum before the experiment.

In addition to these substances, the following ratios were calculated: DOPAC/DA, HVA/DA and 3-MT/DA.

The study was conducted in accordance with Directive 2010/63/EU of 22.10. 2010 and Order No. 267 of the Ministry of Health of the Russian Federation of 19.06.2003.

2.3. Statistical analysis.

The data were processed in Microsoft Exel, MATLAB, STATISTICA 12.6, JASP 0.14.0.0 software. When comparing the data of the experimental groups with each other and with the data of the control groups, the Student's criterion or the Mann-Whitney criterion were used. In case of uneven distribution of the sample, the Mann-Whitney criterion was used, in case of its uniform distribution, the Student's criterion was used. For each comparison, its own significance level was determined (p< 0.001 to 0.05).

3. Results

3.1. Dopamine.

The Mann-Whitney U-test determined that the level of dopamine concentration in the hippocampus four days after simulation of surgical interventions in the nasal cavity, upper jaw and paranasal sinuses, compared with the control, was significantly higher in group 5 and lower in group 4 (p<0.001) (Fig. 2a, Table 1). In group 5, the dopamine level was significantly higher compared to the other experimental groups (p<0.001). In Groups 2 and 4, this indicator was significantly lower than in groups 1 and 3 (p<0.05), which did not differ statistically from each other (p<0.001) (Fig. 2a, Table 1).

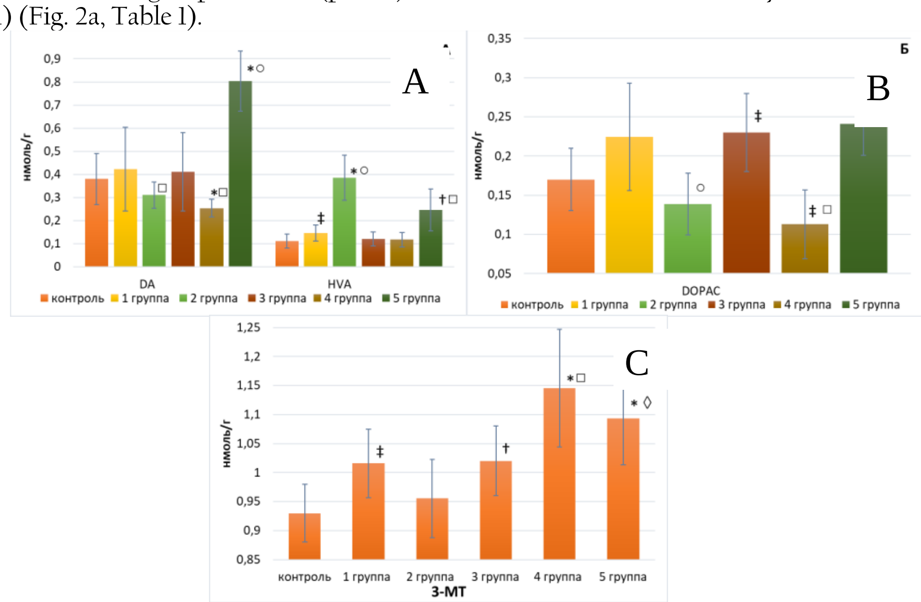

Figure 2. Comparison of the concentrations of dopamine, homovanilic acid (HVA) (A), 3,4-dihydroxyphenylacetic acid (DOPAC) (B) and 3-methoxytiramine (3-MT) (C) in the hippocam-

pus of rats between experimental and control groups. Note: * – a significantly significant difference when comparing experimental groups and a control group at p<0.001; † – a significantly significant difference when comparing experimental groups and a control group at p<0.01; ‡ – a significantly significant difference when comparing experimental groups and a control group at p<0.05; o – a significantly significant difference when comparing experimental groups at p<0.001; o – a significantly significant difference when comparing experimental groups at p<0.01; ◊ – a significantly significant difference when comparing experimental groups at p<0.05.

3.2. HVA.

Evaluation of the concentration of homovanilinic acid in the hippocampus after surgical interventions on day 4 using the Mann-Whitney U-test showed that its concentration was significantly higher in group 2, group 5 (p<0.01) and group 1 (p<0.05) (Fig. 2a, Table 1). An intergroup comparison determined that the concentration of HVA was significantly higher in Group 2, compared with the rest of the experimental groups (p<0.001). In groups 1, 3 and 4, this indicator was significantly lower compared to Group 5 (p<0.01) (Fig. 2a, Table 1). 3.3. HVA.

3.3. DOPAC.

The Mann-Whitney U-test showed that the concentrations of 3,4-dihydroxyphenylacetic acid in groups 3 (p<0.05) and 5 were significantly higher (p<0.01) compared with the control data. The remaining experimental groups did not differ from the control group (Fig. 2b, Table 1).

The level of DOPAC in the hippocampus after simulation of surgical interventions was significantly lower in Group 2 (p<0.001) and in group 4 (p<0.01), compared with the rest of the experimental groups (Fig. 2b, Table 1).

3.4. 3-MT.

Analysis of the content of 3-methoxytiramine in the hippocampus in rats using the Mann-Whitney U-test showed that group 2 did not significantly differ from the control data. The concentration of 3-MT was significantly higher in groups 4 and 5 (p<0.001), as well as in group 1 (p<0.05) and group 3 (p<0.01) (Fig. 2b, Table 1). An intergroup comparison of the concentration of 3-MT revealed that its level was significantly higher in the 4th (p<0.01) and 5th groups (p<0.05), compared with the rest (Fig. 2b, Table 1).

3.5. The DOPAC/DA ratio.

The Mann-Whitney U-test showed that the DOPAC/DA ratio was significantly lower in groups 2 and 4, compared with the control (p<0.001), and this was also noted in group 5 (p<0.01). The remaining experimental groups did not differ from the control group (Fig. 3a, Table 1).

A comparison of the DOPAC/DA ratio between the experimental groups revealed the following. Thus, this indicator in the 2nd and 4th groups was significantly lower than in the 1st and 3rd groups (p<0.001). In the 5th group, this ratio was statistically lower compared to the 1st and 3rd experimental groups (p<0.01), but higher than in the 2nd (p<0.01) and 4th groups (p<0.05) (Fig. 3a, Table 1).

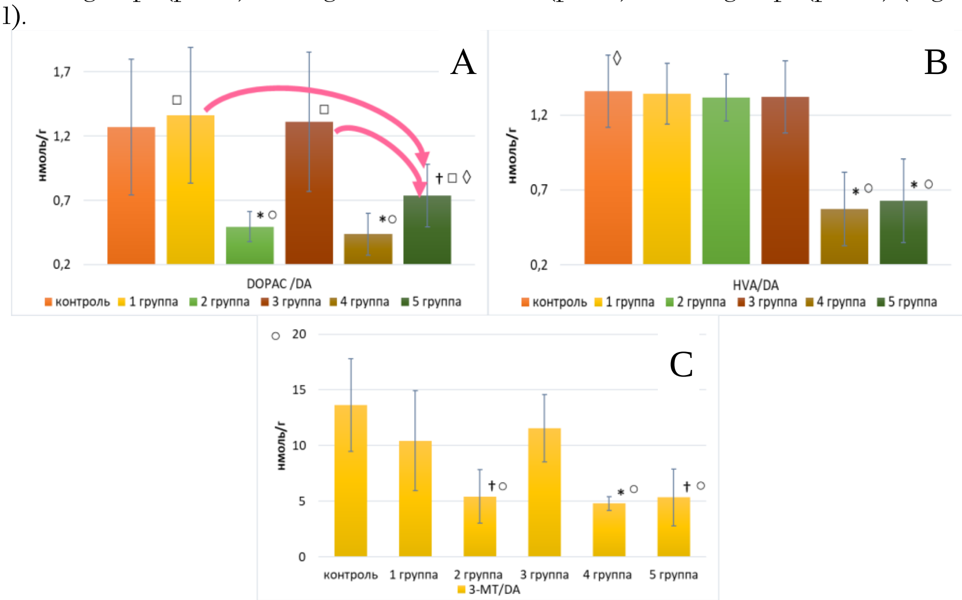

Figure 3. Comparison of DOPAC/DA (A), 3HVA/DA (B) and 3-MT/DA (C) ratios in rat hippocampus between experimental and control groups. Note: * – a reliably significant difference

when comparing experimental groups and a control group at p<0.001; † – a reliably significant difference when comparing experimental groups and a control group at p<0.01; ‡ – a reliably significant difference when comparing experimental groups and a control group at p<0.05; o – a reliably significant difference when comparing experimental groups at p<0.001; – a reliably significant difference when comparing experimental groups at p<0.01; ◊ – a reliably significant difference when comparing experimental groups at p<0.05. Pink arrows – explanations in the text

3.6. HVA/DA ratio.

Evaluation of changes in the ratio of homovanilinic acid to dopamine using the Mann-Whitney U-test showed that, compared with the control group of animals, it was significantly lower in groups 4 and 5 (p<0.001). The remaining groups did not differ from the control (p<0.001) (p<0.001) (p<0.001) (p<0.001) (Fig. 3b, Table 1).

The same was observed when comparing the experimental groups. Thus, the 4th and 5th groups had this ratio significantly lower than in the other experimental groups (p<0.001), which did not differ from each other (Fig. 3b, Table 1).

3.7. The ratio is 3-MT/DA.

The Mann-Whitney U-test determined that in groups 2 and 5 (p<0.01), as well as in group 4 (p<0.001), the ratio of 3-MT/DA was statistically lower than in the control group. The remaining groups did not differ from the control values (Fig. 3b, Table 1). Intergroup analysis using the Mann-Whitney criterion showed that in the hippocampus of rats from groups 1 and 3, the ratio of 3-MT/DA was significantly higher than in the animals of the other experimental groups (p<0.001) (Fig. 3b, Table 1).

Table 1. Indicators of the dopaminergic system of the hippocampus after simulation of rhinosurgical interventions and operations on the upper jaw.

	DA	3-MT	HVA	DOPAC	DOPAC/DA	3-MT/DA	HVA/DA
Control	0,38±0,11	0,93±0,05	0,11±0,03	0,17±0,04	1,27±0,52	13,63±4,16	1,36±0,6
Group 1 (septoplasty)	0,42±0,18	1,01±0,05	0,14±0,03	0,22±0,06	1,36±0,52	10,44±4,49	1,34±0,57
Group 2 (dental implantation)	0,31±0,05	0,95±0,06	0,38±0,09	0,13±0,03	0,49±0,11	5,42±2,39	1,31±0,55
Group 3 (implant bed)	0,41±0,17	1,02±0,06	0,12±0,03	0,23±0,05	1,31±0,54	11,56±3,01	1,32±0,52
Group 4 (sinuslift.+dental implantation)	0,25±0,03	1,14±0,1	0,11±0,02	0,11±0,04	0,4±0,16	4,8±0,63	0,57±0,18
Group 5 (maxillary sinusotomy through the central implant bed)	0,8±0,13	1,09±0,08	0,24±0,09	0,24±0,09	0,73±0,24	5,35±2,56	0,62±0,16

4. Discussion

Under the action of monoamine oxidase (MAO), 3-MT is reduced to HVA and excreted in the urine [18]. The dopaminergic system may be involved in reducing aggressive behavior. Activation of dopamine receptors mediates aggressive behavior, which is caused by electrical stimulation of the hypothalamus [19]. In addition, D2 receptor antagonists weaken aggressive behavior caused by social isolation (SI) [20]. DA is catalyzed to DOPAC by MAO-B, then DOPAC is catalyzed by catechol-O-methyltransferase (COMT) to HVA. However, phytotherapy did not increase the activity of MAO-B in the hypothalamus, which suggests that the HVA content was not associated with an increase in MAO-B activity, and the levels of COMT mRNA were increased as a result of exposure to SI [21]. Other studies have reported elevated levels of COMT in mice that showed aggressive behavior [22]. Since COMT is localized in postsynaptic neurons, an increase in COMT mRNA may be a neuroadaptive response to increased and sustained dopaminergic tone [23].

External stress factors invariably lead to adaptive changes in neurons, which induce sensitization to stress due to a violation of the regulation of dopaminergic and/or noradrenergic systems with activated HVA and cortical response [24].

DA is metabolized by monoamine oxidase to the biogenic aldehyde 3,4-dihydroxyphenyl acetaldehyde (DOPAL) before detoxification by several aldehyde dehydrogenase enzymes to 3,4-dihydroxyphenylacetic acid (DOPAC) [25]. DA and DOPAC modify proteins by self-oxidation of the catechin part to the radical semiquinone or orthoquinone and subsequent addition of Michael to thiols (for example, cysteine) [26, 27]. Similarly, DOPAL can also undergo auto-oxidation of its catechol. It is believed that this self-oxidation increases the reactivity of its aldehyde component [28]. DOPAL also inhibits tyrosine hydroxylase, an enzyme that limits the rate of DA synthesis [29, 30].

It was shown that the concentrations of striatal DA and DA DOPAC and HVA metabolites were significantly reduced in rats injected with 6-OHDA. Tyrosine hydroxylase (TG) is an enzyme that limits the rate of dopamine synthesis, and is mainly expressed in dopamine neurons. Thus, a significantly reduced level of TG protein in the striatum, detected by Western blotting, may reflect damage to the endings of striar neurons and/or death of neurons in SNpc [31]. In another study, it was also shown that a decrease in the level of DOPAC in the cerebrospinal fluid is not only an indicator of Alzheimer's disease, but also a violation of the function of the autonomic nervous system [32]. On the other hand, with post-traumatic stress disorder in the hippocampus, the DOPAC level increases, coinciding with hyperactivation of the noradrenergic system [33].

Extrapolating these data to the present study, it can be assumed that the decrease in the level of DOPAC and the growth of p53-positive neurons, as well as an increase in apoptosis of neurons, in all subfields of the hippocampus are interconnected and may indicate a high level of exposure to sinus-lifting surgery with immediate dental implantation. An increase in the level of DOPAC, compared with the control, was noted in the groups of septoplasty, implant bed and maxillary sinusotomy through the implant bed.

Tissue 3-methoxytiramine (3-MT) accumulated within 10 minutes after monoamine oxidase inhibition can be used as an indicator of terminal dopamine release [34, 35]. Especially its concentration increases with damage to the ventral hippocampus in rats [35].

There is consistent evidence that the release of dopamine acid in the prefrontal cortex during stress suppresses subcortical release of dopamine [36].

Using a microwave fixation system, a significant decrease in DA, 3-MT and HVA was found in the striatum of R6/2 mice aged 8 and 12 weeks, parallel to the motor deficit in these mice [37, 38]. Some of the dopaminergic changes were also observed in areas unrelated to the striatum, such as the hippocampus and frontal cortex, which highlights the early aberrant connectivity of dysfunctional frontal striatum circuits in Huntington's disease [37]. Similarly, several studies have reported a decrease in the level of HVA in cerebrospinal fluid in patients with Huntington's disease prior to the identification of the HTT gene [39]. A decrease in the ratio of 3-MT/DA and HVA/DA in the context of a decrease in DA levels [40] is consistent with more direct measurements of a decrease in dopamine release [41- 42].

It is known that DA plays an important role in the functioning of the central nervous system, influencing various manifestations of mental activity of animals and humans [43]. It has been shown that brain processes involving DA are significantly disrupted during the development of depression [44].

The introduction of dopamine receptor agonists and antagonists into the hippocampus, respectively, improves and worsens hippocampal-dependent learning (45, 46). This fact can be applied to the present study in the context that a significant release of dopamine may indicate a large surgical alteration, provoking a cascade of adaptive reactions that can be aimed at improving the behavior and memory of an animal under stress.

The greatest increase in 3-MT was observed in groups 1, 3, 4 and 5, compared with the control. Considering that in DA it is metabolized in 3-MT and DOPAC in different ways with the help of COMT and MOA enzymes, respectively, it can be assumed that a higher level of dopamine cleavage to 3-MT was observed in all groups except the dental implantation group. An increase in DA metabolism along the DOPA pathway was noted only in the groups of septoplasty, sinus-lifting with dental implantation and complicated sinus-lifting with maxillotomy. It can be concluded that the release of dopamine in the hippocampus, as a neurotransmitter acting on D1/D5 dopamine receptors and inducing long-term potentiation of pyramidal neurons of the CA1 subfield under afferent stimulus from the Shaffer collaterals, can be considered as a defense mechanism (potentiation, improvement of learning and memory) under surgical stress, on the one hand, and the manifestation of inadequate hyperimpulsation into the hippocampus region with an increase in disadoptation reactions, on the other hand [47].

The HVA/DA, DOPAC/DA relationships may reflect the activity of pre-familergic brain activity [48].

Chronic stress is associated with increased levels of norepinephrine (amygdala and hippocampus) and dopamine (HVA/DA, DOPAC/DA) in the prefrontal cortex [49, 50]. Thus, chronic stress provokes a decrease in HVA/DA, DOPAC/DA. In another study, using the example of chronic stress in rats, it was shown that DOPAC levels in the frontal cortex and in the hippocampus increased, in addition, an increased ratio of 5-HIAA/5-HT was observed in the hippocampus. In the hypothalamus, HVA and DOPAC levels were reduced, as well as the DOPAC/DA ratio. Chronic stress caused a decrease in the mass of the adrenal glands. It has been found that chronic variable stress causes a decrease in dopaminergic neurotransmission in the hypothalamus. Elevated levels of dopamine metabolites in the cortex and hippocampus were also observed [51]. During handling in male rats, the level of DA of its metabolites increases, which is expressed in an increase in DOPAC/DA in the hippocampus [52].

In the hypothalamus under chronic stress, there is a decrease in dopaminergic activity, as evidenced by a decrease in the HVA/DA and DOPAC/DA ratios [51]. The decrease in the ratios of 3-MT/DA and DOPAC/DA in the present study in the 2nd, 4th and 5th groups, as well as HVA/DA in the 4th and 5th groups, indicates that the after simulation of surgical interventions in the upper jaw, as well as in the area of the maxillary sinus provokes a high stress response, which goes into the phase of maladaptation.

5. Conclusions

After simulating sinus lifting with immediate implantation and dental implantation complicated by maxillary sinusotomy, there is an increase in the concentration of dopamine metabolites 3-MT, HVA and DOPAC, but at the same time a decrease in dopaminergic activity of the hippocampal formation, compared with simulation of septoplasty and simple damage to the alveolar ridge of the upper jaw. Most likely, such changes are explained by the disruption of the adaptive response in the early postoperative period in the absence of analgesic therapy and correction of stress reactions.

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