GENETIC AND EPIGENETIC PROGRAMMING OF HUMAN SOCIAL PSYCHOLOGY AND BEHAVIOR. OXYTOCIN RECEPTOR GENE.

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Summary

The assertion is substantiated that the response of an individual to the changes in the social environment is determined by a genetically inherited system of cell groups with oxytocin receptors, OXTR. Each group of OXTR cells exhibits distinct pattern of connections with other brain cells and plays a distinct role in the response of the organism to changes in the social environment. The brain switches between groups of cells. The switching is completed by concurrent effect of epigenetic mechanism of methylation of the gene OXTR promoter and mechanism of histone acetylation in the area of this gene.

The past decade and a half studies have shown that genes of oxytocin and vasopressin receptors in the brain play a leading role in the social recognition, social memory and in person's social behavior. These amazing patterns pose the question that lies at the heart of human adaptation to changing conditions of social environment. In previous publications (B. Fuks, B. Berel, 2013, 2010) we used the following scheme: three pairs of genes are controlling person's social behavior - gene of oxytocin receptor and two genes of vasopressin receptor. We proceeded from the fact that alleles of these genes form three possible combinations: homozygous altruists, homozygous egoists and heterozygous group containing positive and negative alleles of these genes. Today, five years later new data are obtained that require elaboration of the scheme and aftermath. It must also be clarified if new data do confirm the hypothesis of division of every human community in three above-mentioned groups with differing behavior, or things are more complicated. The aim of this study is to find the answer to the question of how and when the impact of environmental social factors on man leads to reversible epigenetic behavior reprogramming of an individual or group of individuals, adequate to external signal. Simply put, what is the mechanism of adequate changes in gene activity in this group in person influencing by family, school, and church, social or antisocial propaganda. The term "reprogramming" is used, based on the findings of a number of social processes that have occurred in several countries in Europe, America and Asia in the postwar period to the present day. We have in mind primarily the obvious changes in mentality of German and Japanese people – abandon of aggression. Obvious are changes in the mentality of the people of the United States, meaning the overcoming of racial intolerance and liberalization of social life - sometimes too much. Examples could go on, but the main issue in relation to the plasticity of social behavior can be formulated this way: what are the limits of this plasticity. Why plasticity of social behavior of a few individuals to face insurmountable obstacle, and they retain their behavior in society even under threat of imminent death. It is specifically talking about righteous group of the world, people like Irene Sandler and Lieutenant Nikolai Kiselev. We do not have data on the importance of gender differences. Rubin L.H. at al. (2017) have determined that there are gender differences in intracerebral activities, particularly in regions that are important for processing emotion and cognitive abilities, including prefrontal, temporal and parietal areas. The authors have shown that OT and AVP may modify the physiology of the brain in these regions, helping to reduce but not increase gender disparities. Therefore we should accept that these regions are rich in the human oxytocin receptors- OXTR.

Oxytocin receptor (OXTR) gene alleles. Stress induced epigenetic switching mechanism.

Oxytocin Receptor always mediates action of this hormone on brain. According to Simmons CF. Jr et al. (1995) alleles of oxytocin receptor gene in humans are located in chromosome 3r25. Detailed description of the gene and its receptor protein product exists in databases. As stated by Saphire - Bernstein S. at al. (2011) in human chromosome 3r25 rs5376 polymorphism occurs in the third intron of OXTR gene. There are three types of it: GG, AG and AA. We are talking about two alleles of OXTR gene; homozygous and heterozygous individuals with different social behavior are known. As claimed by Kang, h. j. et al. (2011) OXTR transcriptome analysis showed a progressive increase OXTR mRNA during embryonic life in five out of six of the analyzed areas of the brain. According to Grinevich V., et al. (2015), it is noteworthy that the receptor level reaches its maximum before birth and remained rather stable thereafter, at least for the first 5 years of life, albeit with some variations. OXTR gene is associated with depressive symptoms. People with the A allele do not tolerate stress; have fewer social skills and more mental health problems than people with GG allele. In humans the GG allele is associated with oxytocin levels in the body (Shimon Saphire-Bernstein, at al., 2011)

The SNP-oxytocin receptor gene (OXTR), rs53576, is associated with the change of social functions when guanine (G) is replaced for adenine (A). The presence of allele (G) not only contributes to the prosocial behavior, but also reduces human sensitivity to negative social influence. "We and others have found that oxytocin acts as a neuromodulator disinhibitory throughout the brain" claims Mariela Mitre al, in their paper "A Distributed Network for Social Cognition Enriched for Oxytocin Receptors", J. Neurosci.. 2016 Feb 24; 36 (8): 2517-2535. According to Michal Chorev and Liran Carme (2012), the level of gene expression is determined by introns; in particular, they affect the amount of produced mRNA as well as different stages of the mRNA splicing and protein synthesis. It worth looking into speculation that GG allele determines higher levels of oxytocin receptor gene expression compare to people with AA alleles, which can determine prosocial effect on individuals with GG alleles. These individuals are prone to altruistic behavior. People with AA alleles are not altruistic. Higher levels of oxytocin receptor gene expression can have functional expression, i.e. leads to increase of the number of oxytocin molecules, associated with any given cell per time unit. Oxytocin is a small molecule with molecular weight of 1007 Da (C43H66N12O12S2), and OXTR is a large one. In the mammary gland and uterus, it has a molecular weight of 57.5 +/- 3.8 and 59.2 +/-1.6 kDa respectively. We have not found similar data for the brain OXTR, but considering that the genome has only one OXTR gene, we can assume that in the brain this protein has the same molecular weight. Shimon Saphire-Bernstein et al. (2011) report the connection of SNP rs53576 oxytocin receptor gene (OXTR) with psychological resources. Allele carriers have lower levels of optimism, mastery and self-esteem, compared with GG homozygotes. Many authors associate polymorphism in oxytocin receptor gene (OXTR), rs53576, with socially significant positive personality traits and behavior. Nevertheless, the published results are inconsistent. Li and coauthors (2015) conducted a meta-analysis to fully assess the association. They searched for data on the relation between individuals with homozygous allele G (GG) and carriers of alleles (AA/AG). In particular, the two indices of sociality were evaluated independently: 1) sociality in general (24 studies, n = 4955), that is, how a person reacts to other people in general; and 2) a close relationship (15 research, n = 5262), that is, how a person reacts to close related people (parent-child or romantic relationships). A positive relationship between polymorphism rs53576 and general sociality was found (Cohen's d = 0.11, p =. 02); allele G homozygotes were characterized by higher sociability compare to rs53576 carriers with close relationships between people (Cohen's d = 0.01, p =. 64). Their conclusion was modest: genetic variability in rs53576 affects the general sociality.

There have been reports that differ from widely accepted. So David H. Skuse, et al (2014) reported that another SNP (rs237887) in oxytocin receptor is closely linked with recognition memory. The results of the authors also indicate the critical role of oxytocin system in social recognition. Polymorphism in the oxytocin receptor gene (OXTR) was associated with skills of social recognition. rs237887 SNP is also located in intron 3 of OXTR gene. It is located in the block that contains three other SNPs, being in a moderate dependency with them. The initial analysis suggests the genetic relationship between the SNP rs237887 and face recognition memory exists in not only studied individuals, but also their parents (of both sexes), and their brothers and sisters. The authors did not find any significant link between the SNP rs53576 and defined endophenotypes, although other authors relate this specific SNP with a number of OXTR properties associated with cognitive and social characteristics. Authors associate SNP rs237887 with personal empathy, autistic traits and emotional and behavioral reactions to betrayal. Confidence in the accuracy of such findings is enhanced by the presence of the same degree of association between this SNP and face recognition memory. The main hypothesis of the study is as follows: there is a relationship between SNP in AVPR1A and OXTR and three endophenotypes in regards to social cognition (face recognition memory). However, there are no supporting studies yet.

Data about the asocial behavior of individuals with pro-social OXTR gene alleles under social stress are important. The role of this gene polymorphism in antisocial behavior is vaguely studied, in particular during the transition from adolescence to early adulthood. Smearman E.L., et al. (2015) studied disorganized/unsocial behavior in group of youngsters (15 -20 years old, n = 404), their mothers and analyzed their medical reports. Authors suggested that under social stress the rs53576 polymorphism will produce asocial behavioral results. The effect was mostly pronounced at the age of 15 years ($p = 0.025$); among those with allele G the higher levels of negative behavioral problems were observed. Structural equation modelling identified a significant interaction of this gene with the social environment for 20 year old individuals ($p = 0.029$). Those with G allele, who experienced high negative social strain, showed higher levels of asocial behavior.

These new data show that rs53576-polymorphism may contribute to the risk of asocial behavior, especially at high social tension conditions. In the absence of stress G allele provided prosocial behavior of young people. Under the stress the same allele contributed to asocial youth behavior. According to the authors, the asocial behavior is a threat to others, the destruction of or damage to property, violation of the rules, lying, swearing. Chronic stress occurred during the past 6 months with the assessment of the gravity on the 5-point system with clamping weights in each of several domains: social life, close friendships, romantic relationships, and relationships with family members, academic achievement, professional experiences, personal health and that of close relatives. The authors have shown that GG individuals more often exhibit asocial behavior during strong social stress than people with AA alleles. In the subgroup of 20 year old individuals OXTR polymorphism study at different levels of social stress revealed that G carriers show higher levels of anti-social behavior only in the presence of high social stress, whereas persons with AA-alleles not significantly differed in asocial behavior at different levels of social stress. Also, oxytocin (OXT) involved mainly in prosocial behavior, like the trust and generosity. However, these effects are highly dependent on the characteristics of the situation and people involved in interaction, and when they make a decision. Rules and regulations can promote and guide these activities. Justice is particularly important, even becomes a main rule. Sina Radke et al. (2012) investigated the effect of intranasal administration of OXT on justice in social decision-making in a double blind, placebo-controlled experiment. Results are as follows - asocial in social situations when other members are perceived as not belonging to their group. These results confirm the view that the effect of OXT is more nuanced than previously thought.

M. Nahajima et al. (2014) showed samples of stellate cells with OXTR in the cortex of the brain. Cells had multiple dendrites and neurite. If in any particular cell GG allele is expressed, in a calm situation its neurite has a contact with nerve cell, involved in implementing the prosocial behavioral function. There is an apparent paradox: such a cell, in which the GG allele of OXTR gene is expressed, cannot quickly switch to execute the asocial function under the stress (see Smearman EL et al). This OXTR cell apparently is not in synaptic connection with any other brain cells involved in the asocial function. In addition it has a single axon. Almost every region of the brain has its "own" OXTR cells. This can be seen by cytochemical detection OXTR cells in the brain. If you follow the model of Smearman E.L. et al., the question how other OXTR cells are engaged under the stress, i.e. the issue of the mechanism of such a switch, cannot be ignored. To answer this question, the epigenetic mechanism was proposed. Meghan H. Puglia et al., 2015 stated: «Importantly, this epigenetic modification- OXTR methylation-directly impacts the expression of oxytocin's receptor, which is critical for the actions of oxytocin to have an effect". When a response to the stress (in the work of Smearman E.L. c et al) occurs through the epigenetic mechanism (only?) new OXTR- cells are involved (see Figure 1), in which also GG allele is expressed as may be expected. This possibility does not contradict the data from Mei-Lyn Ong (Novel region discovery method for Infinium 450K DNA methylation data reveals changes associated with aging in muscle and neuronal pathways (Aging cell, 22 October 2013).

Fig. 1. Scheme. Two options for the location of OXTR cell groups

The foregoing demonstrates plasticity of OXTR cell system, but is not bringing us closer to the explanation of the cases (individuals) when adaptation to the changing social environment is completely missing. In the brain there are places where OXTR cells are condensed, however differently in different species. In the study by Mariela Mitre et al., (2016) compactness was not mentioned. Electron microscopic study of murine cerebral cortex by these authors showed that oxytocin receptors mainly expressed in synapses, as well as axons and glial processes. Another question arises about the "reason for the brain" to have such places of compact OXTR cells system (Figure 2) when targeting oxytocin delivery to them is not accurate. Histochemical data suggest that OXTR-cells form groups with different functions. However, adaptation to the new social environment, i.e. plasticity, is not implemented in a specific group of people, which we outlined at the beginning of this article. Special interest is the people who programmed in the way it was consistent with the world righteous group. Above we have sought to explain the possibility of relatively rapid reprogramming of not just one person, but also groups of people from prosocial to an asocial behavior without any changes in oxytocin receptor gene alleles.

A brief digression to define terms

In psychology we often use the terms "prosocial", "asocial" and " antisocial ".Prosocial behavior: voluntary behavior, aimed to benefit of others, or to benefit of society as a whole; such as help, the desire to share, donations, inclination to cooperate and voluntary work; behavior that is positive, helpful, and intended to promote social acceptance and friendship. Asocial behavior leads to isolation from other people, person avoids social interaction, is inconsiderate or even hostile towards other people. Antisocial behavior: a person performs actions against the laws and customs of society, antagonistic to social instincts or practices. It is a dangerous, unscrupulous type of person, not outgoing, not wishing to be in the company of other people. Antisocial behavior is like a separate complex. These include serial killers and serial rapists. Thus, if asocial

behavior is elimination from a society, antisocial one is an action (often violent) against humanity. Unfortunately, some authors do not adhere to this classification and use the terms an asocial and antisocial as identical.

According to Smearman EL et al. (2015), prosocial behavior occurs when one type of the GG cell Groups is associated with a particular neuronal structure, and other groups of GG-cells are in communication with other neurons when switching them to asocial behavior. The alternative assumption that switching from prosocial to asocial behavior is determined by crucial alteration of synaptic contacts between the same pool of OXTR-cells and the cells of different neuronal structures, that is unlikely. It follows that oxytocinergic system consists of not the same morpho-(?) functional groups of OXTR cells. Such a design should maximize human adaptation in the social field. Two socially important OXTR alleles are described. Alleles are encoded in the third intron of OXTR gene. We noted above that introns affect different stages of gene expression (Michal Chorev and Liran Carme (2012), as well as the final stage - protein synthesis, in the present case, synthesis of oxytocin receptor. These may include a number of oxytocin receptor molecules, and as a result - two types of social behavior of individuals. The behavior of people with AA allele described as not prosocial and egoistic, but by no means as asocial. However, asocial behavior occurs under the social stress and namely in the presence of GG allele (Smearman EL et al, 2015). We conclude that there is a switch of activity from one prosocial GG-OXTR cell group to other asocial GG-OXTR group of cells. These studies by Smearman E. L. et al. (2015) let to take a detached view on the OXTR cell group system. Certain OXTR cells associated with a particular polyneuron structure, specialized to perform a certain function in the social behavior of an individual. Under the influence of stress a new complex is involved: other OXTR cells and other polyneuron structure. They provide asocial individual behavior. Smearman EL et al. essentially provided data on existence of at least two different morpho (?) functional complexes incorporating OXTR cells. These complexes are associated with oxytocin-producing cells, which are not exactly (!) projected onto a certain group of OXTR cells, which in turn are associated with a certain polyneuronal structure, performing specific effector functions. There is a structure with a plus sign. In this structure GG allele of the oxytocin receptor gene works positively. Another GG-OXTR complex with similar structure can perform asocial functions, i.e. with a minus sign. They can be different not only functionally, but also structurally. People with AA and AG alleles also have AA and AG OXTR groups of cells. However, according to Smearman EL et al. (2015) personalities with such alleles do not react to stress by involvement in asocial behavior.

Thus the following structures can be visualized in the brain. First of all, it might be a structure consisting of the cells-producers of oxytocin, OXTR cells and other related brain cells. The structure performs a positive behavioral function. Secondly, the other similar morpho-functional OXTR group(s) of cells; they are associated with other brain cells, are supplied with oxytocin by cells-producers OXT and perform negative behavioral function. Returning to the question raised at the beginning of this article, let's note that human population consists of two homozygous and one heterozygous group regarding OXTR gene alleles. Homozygous AA group is not responding to the stress by asocial behavior, as it happens with homozygous GG group. Asocial actions are not possible without the involvement of new groups of nerve cells, which were associated with other OXTR -cells prior to the stress. It is about the involvement of another OXTR group. This claim, in particular, comes from the fact of prevalence OXTR cells in brain regions with pronounced compactness of OXTR- cells distribution (cytochemical analysis). Apparently, it is impossible for one restricted group of OXTR cells to have synaptic contacts with numerous neurons in many other remote regions of the brain. Morphological analysis shows that different regions have their "own" OXTR cells. Recently, Maroun M. and Wagner S. (2016) concluded that numerous roles of oxytocin in social behavior and sense of fear is the

consequence of its local effects in different parts of the brain. It is important that asocial actions can be controlled by GG allele of OXTR gene and does not occur under the control by AA allele. Insight is emerging that the difference between the alleles associated with a defective receptor expression in individuals with AA alleles. This suggestion is verifiable.

In real life during the last hundred years it has been a lot of reprogramming events of large groups of people, which was making them dangerous for mankind, and then reverse reprogramming – a return to social norm. Presumably these events are based on epigenetic changes of major social behavior genes: OXTR gene and vasopressin receptor (V1a and V1b) genes.

Cells - producers of oxytocin

OXTR receive oxytocin from the hypothalamus. McGregor IS et al (2008) showed that the oxytocinergic cycle includes projection of axons from the paraventricular nucleus of the hypothalamus (PVN) in ventral tegmental area (VTA) with innervation dopaminergic neurons, which, in turn, innervate nucleus accumbens; i.e. we are talking about mezolimbic pathway. Activation of the PVN→VTA projection by oxytocin affects prosexual and prosocial behavior via this link to the mesolimbic pathway. According to Vishruti Makani and others (2013) pro-oxytocin is synthesized in the cell bodies of neurons in supraoptic and paraventricular hypothalamic nuclei. Oxytocin then turns into a mature form consisting of 9 amino acids after passing through the Golgi apparatus. Oxytocin then moves into the axon and somatodendritic regions of the same cells. From somatodendritic regions oxytocin penetrates the cell membrane and is diffusely distributed across the whole hypothalamus and neighboring regions of the brain. There is not an exact address delivery of the hormone, and means an increased involvement of OXTR groups of cells. Oxytocin binds to receptors on the OXTR -cells in areas of the brain involved in social behavior of a man. Oxytocin also is secreted from the posterior pituitary into the blood. Vishruti Makani et al (2013) describe the molecular complex consisting of anneksin A1 (ANXA1), A-kinase, anchor protein 150 (AKAP150) and microtubules; this is the motor that controls the distribution of oxytocin vesicles between the axon and the producer's cell body. It is accepted that the neuropeptide oxytocin is a tool (together with a vasopressin) that the brain uses to ensure rational human interaction with other people and with the society of others. Oxytocin cells producers send it through axons to the cells with oxytocin receptor. The last, in turn, send directed signal to structures responsible for one or the other option of social behavior. Naturally, that freely spread oxytocin can activate only the cells with OXTR, which involve certain brain cell structures in social recognition and action. Now it is possible only approximately outline what are these "certain cellular structures". Quoted above Maroun M. and Wagner S. (2016), believe that multiple roles of oxytocin in social behavior and fear is still a result of its local effects in different parts of the brain.

Methylation of OXTR gene promoter

DNA methylation is a chemical post-replication modification of CG dinucleotides, which covalently binds methyl group (CH3). DNA methylation is catalyzed by DNA-methyltransferases. Methyl group binds to the fifth carbon atom of cytosine in CpG site. Regions with high frequency of CG sites known as CpG islands and are usually located in gene promoters. Since the process of DNA methylation involves enzymatic attachment of methyl groups to CpG dinucleotides, it requires methyl donor compounds. Methyl groups are obtained from the diet. Conventional sources are folic acid, betaine and vitamin B12. The presence of these compounds ultimately affects the metabolism of methionine and S-adenosylmethionine (SAM), which has methyl group and is the main donor for several methyltransferases. (Labome, 2013)

So, genome DNA methylation is a universal event. It is catalyzed by methylases (DNA methyltransferase). Along with this DNA demethylation occurs, acetylation and deacetylation of amino acids in histones (acetylase, histone acetyltransferase) (Rudolf Jaenisch's group & Adrian Bird, 2003). We are talking about epigenetic mechanism of realization of orders coming in OXTR cells. The source of signals-orders is an environment and then brain cells (Wade M, Hoffmann T.J., Jenkins JM, 2015). In total, this complex is adapted to perform core functions - recognition of "his" or not "his", etc. and effector reactions under the influence of oxytocin. These features apparently define a prosperous or even physical survival of the individual in society. Listed events are the subject of numerous works now. The main known mechanism by which DNA methylation can regulate gene expression is the prevention of binding DNA with the factors, contributing to the transcriptional activity. Meghan H. (2015) studied the oxytocin receptor gene DNA methylation. Higher levels of methylation of OXTR gene were associated with increased nervous reactions and decreased functioning of the regions that support social perception and handle emotions. This version of activity demonstrates lowered emotional reaction to negative stimuli. DNA methylation of OXTR is an epigenetic change, which directly affects the transcription of the gene and is variable. The authors found a link among OXTR gene methylation, neural activity and emotional activity of person's face. In particular, high level of OXTR gene methylation also was associated with pronounced activity in the regions, affecting the facial expression (amygdala, fusiform, and insula). Higher levels of OXTR gene methylation also were associated with a reduction in the functional interaction between the amygdala and the regions involved in the affect evaluation and emotion regulation. The authors believe that a system of endogenous human oxytocin participates in weakening the reactions of fear, which is confirmed by studies with intranasal administration of oxytocin. Shimrat Mamrut, et al. (2013) made an impressive analysis of what methylation and demethylation of SpG islands in OXTR gene promoter signifies. Univocal conclusion is: the function of this gene is regulated, i.e. the strengthening or weakening of transcription. Robert Kumsta et al (Frontiers in Neuroscience 23 May 2013) report that the structure, which includes the CpG was suppressed at 70% after methylation. I.e. in CpG islands OXTR transcription was suppressed. But these experiments were conducted on hepatoblastoma cell line. Kusui et al. (2001) have identified the region of CpG islands OXTR MT2, which was responsible for the silence, triggered by methylation. MT2 deletion saved 68% of transcription of methylated structure. Differential methylation of the CpG island in OXTR promoter is important for OXTR expression.

There is a chain of events: external to the organism factor actuates the brain, and then epigenetic mechanism in the brain is initiated. Its last link, methylase-demethylase, demethylates DNA of OXTR gene and histone acetylation occurs. Then gene transcription follows. An amplification of OXT action on neurons, which are synaptically connected to OXTR cells, occurs through expressed OXTR gene. As of today, the last two steps of epigenetic mechanism are well studied: enzymes methylases and acetylases as well as the process of histone acetylation and DNA methylation. An attempt to allocate other parts of epigenesis made in the study on newborn rats by J. Meaney (2011). But the elucidation of the role of these parts in the human brain is outside the technical possibilities at the moment. This investigation gives an impression that epigenesis is not "above genetics" but in the form of molecular inclusions incorporated into neuro-humoral regulation mechanism. Perhaps it is some ancient regulation mechanism existed before the emergence of the nervous system. Let's quote here a fragment of interest from the study by J. Meaney on newborn rats.

"Tactile stimulation derived from maternal licking appears to be the critical signal for the regulation of hippocampal GR expression and HPA responses to stress. Indeed, within-litter variation in the frequency with which individual pups are licked is significantly correlated with

hippocampal GR mRNA levels in adulthood [40]. Finally, artificial tactile stimulation of rat pups, which mimics that afforded by licking, increases hippocampal GR expression [38].

The results of in vivo studies with tissue samples from rat pups or in vitro studies using cultured primary hippocampal neurons suggest that maternal effects on GR expression are mediated by increases in hippocampal serotonin (5-HT) activity and the expression of the transcription factor, nerve-growth factor-inducible factor-A (NGFI-A) [41–46]. In vitro, 5-HT increases the activity of cAMP-dependent signaling pathways in hippocampal neurons through the activation of a 5-HT7 receptor resulting in elevated expression of the transcription factor, NGFI-A. Activation of this signaling cascade leads to increased GR expression. The effect of 5-HT on GR expression in cultured hippocampal neurons is (1) blocked by 5-HT7 receptor antagonists or compounds that inhibit the activation of protein kinase A, (2) mimicked by 5-HT7 receptor agonists or treatments with stable cAMP analogs (e.g., 8-bromo-cAMP), and (3) eliminated by concurrent treatment with an antisense directed at the NGFI-A mRNA [45, 46]. In vivo, the increase in hippocampal 5-HT activity is associated with a maternally-regulated increase in the conversion of thyroxine to triidodithyronine (T3) [46]. T3 regulates the activity of ascending 5-HT systems and neonatal administration of T3 mimics the effects of increased pup LG on hippocampal GR expression [47]. In vivo, T3 administration increases hippocampal NGFI-A expression [48] and this effect as well as that on GR expression are blocked with 5-HT receptor antagonists [46] (Hellstrom and Meaney, unpublished).

The DNA site at which maternally regulated, 5-HT-induced NGFI-A signal alters GR expression involves distinct regions of the 5′ non-coding variable exon 1 region of the hippocampal glucocorticoid receptor gene (Fig. 2). This region contains multiple alternate promoter sequences including the exon 17 sequence, which is highly expressed in brain [49]. Increased levels of pup LG enhance hippocampal expression of GR mRNA splice variants containing exon 17 [45], suggesting greater transcriptional activity through this promoter. The exon 17 sequence contains an NGFI-A response element [49, 50]. Pup LG increases hippocampal NGFI-A expression and chromatin immunoprecipitation (ChIP) assays, which permit quantification of protein interactions with specific DNA sequences, with hippocampal samples reveal increased NGFI-A association with the exon 17 promoter in pups of High compared with Low LG mothers [45]. Co-transfection studies reveal NGFI-A-induced activation of transcription through the exon 17 promoter [45]. The effect of NGFI-A is eliminated by a site-directed mutation within the NGFI-A response element of the exon 17 promoter [45] such that the physical interaction of NGFI-A with its response element triggers transcriptional activation. Infection of hippocampal neurons with an NGFI-A expression plasmid increases both total GR mRNA and exon 17-containing GR mRNA [46].”

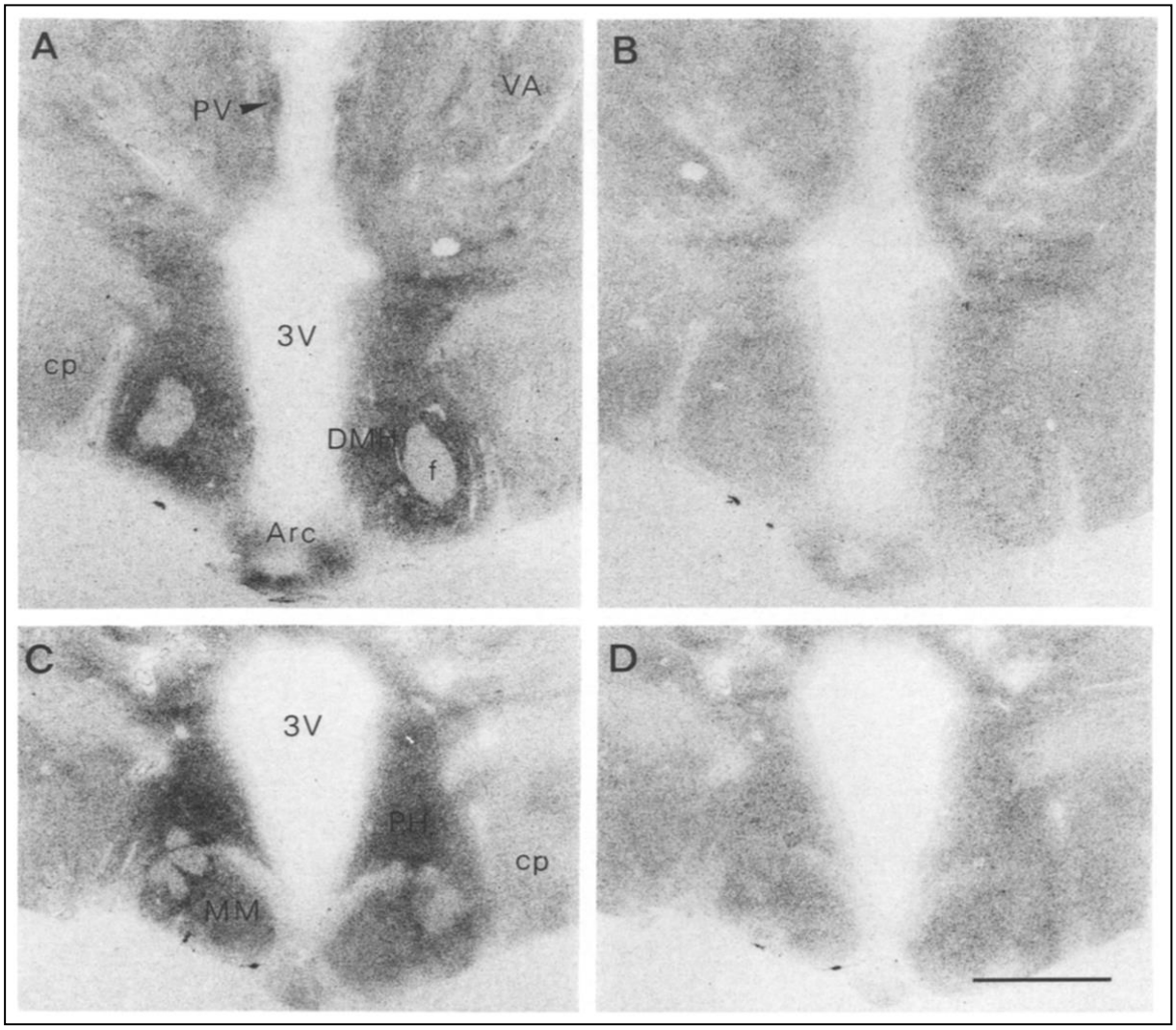

Fig. 2. Microphotography. Areas of ^{125}I-oxytocin binding on anterior human thalamic slices (A,C). B and D (on the right) - two similar control slices: unlabeled oxytocin was added to the labeled ^{125} I-oxytocin and incubated. (F. Loop et al., Brain research, 1991.)

The above extremely complex text is raising questions. How a coordination of these processes occurs in micro space and time. Only one thin fibrous nervous-cellular tissue is known, which coordinates processes in the brain and periphery. Adequacy of organism response, amazing in the studies by Meaney group doesn't seem equally amazing in studies of an object- individual- personality. External environment and its changes constitute signals delivered through sensory organs, which are adequately processed in the human brain and the resulting activity is distributed to OXTR genes in certain cells with oxytocin receptors. Solution in which particular groups of cells the OXTR gene will be fully activated obviously should take a brain in toto.

In the ontogenesis the mosaic acetylation-deacetylation and methylation-demethylation of OXTR promoter is changing (Kumsta R. et al 2013). Different mature individuals of the same species also differ in this regard (Kumsta R et al. 2013). Considering the role of OXTR in human social behavior, an assumption can be made that the inherited mosaic of acetylation-deacetylation of histones and methylation –demethylation of DNA of OXTR promoter in the pool of cells with OXTR in the brain defines the person's social behavior. It is obvious that the same applies to an extreme form of the behavior-to the righteous of the world. Epigenetic

mechanism described above undoubtedly involved in the formation of behavior of these unusual people, because it is universal in the genome of the OXTR cells.

In the work Loup F. et al. (1991), localization of oxytocin and vasopressin receptors in the brain of 12 people was researched post mortem using the autoradiographic method. On figure 2 is an area of localization of the receptors in the brain. Localization of two receptors in the brain stem and upper part of spinal cord were not the same, although overlap in the spinal cord. Unlike other mammals, particularly high receptor concentration was in the nucleus basalis of Meynert and in the area of Broca. Important for us is the information that receptor localization is not the same in different people. Thus, in the area of the island of Calleja oxytocin receptors have been found in only two of the seven investigated cases. In many cases, the authors have reported inconsistent faint weak concentration of receptors in such-and-such place in different brains.

We postulate that a group of cells with OXTR in the brain are functionally varied and that switching from one group to other group lies at the core of personality reprograming of its social behavior. Data presented by Loup F. et al. (1991) are supporting such a view, because they suggest different locations of receptors in the brain of different people. While different groups of OXTR cells may have different connections in the brain.

The foregoing leads to the assumption that the variability in the location and relationship of groups of OXTR cells is an important reason for the diversity of social behavior of individuals. The same reason is bringing into the existence individuals with extreme social characteristics. For example, righteous of the world.

Apparently there are no new similar studies on human brain. They are absolutely necessary to prove an important assumption made above.

Information, calling for specific actions is taken by the higher brain, neurons that are in the synaptic links with the cells expressing or ready to express OXTR. Epigenetic mechanism and its very last links turn on, in particular, the enzyme that demethylates DNA promoter of OXTR gene. OXTR is expressed on the surface of such cells and under the influence of oxytocin they begin to activate synaptically connected new effector neural structure. In the same way the new group of OXTR cells can be involved.

DNA methylation is a reversible process. Therefore, DNA methylation of OXTR gene cannot be stable. This is a dynamic process, which at any moment is regulated by signals to OXTR cells. Oxytocin and OXTR are “used by evolution to" centralize the management of social behavior, and perhaps to increase a power and agility of control system, as well as to implement a fine "tuning" of this system to events in the environment. In the light of the above, reprogramming is based on switching from one OXTR-complexes of cells to the others and the formation of a new homeostasis.

Distribution in the society of the three allele options (GG, AG and AA) allows predicting the social behavior of individuals, belonging to three different groups. The circumstance that a switch of AG and AA -individuals on asocial behavior does not occur, and switching GG - individuals occurs under a social stress can be contingent to quantitatively varying gene expression. However, it needs to be experimentally confirmed, which was not done yet. Above we found the arguments that reprogramming is always switching from one (or some) OXTR complex cells to another. Thus the plasticity of oxytocin-OXTR system in the brain is carried out. The existence of plasticity clarifies reprogramming events of the masses of people in different directions, and deviations of social behavior in the XX century (Nazism, fascism, communism, internationalism, racism, and nationalism).

The answer to the question about the real mechanism of social reprogramming of personality probably cannot be found in the sphere of dynamics of so-called CpG islands in the OXTR gene promoter only. These islands of DNA are relatively resistant to methylation. Meanwhile methylation (see above) is credited to a special role in the functioning of this gene. Here is a quote: "These results suggest that OXTR methylation affect relatively low level processes involved in social perception and interindividual differences in social recognition and behavior" (Robert Kumsta et al., Frontiers in Neuroscience 23 May 2013). This assertion does not allow you to understand the reason of namely interindividual differences. There is a lack of some link. In addition to the methylase histone acetylases operate in the immediate vicinity. Their role in the functioning of the human OXTR gene apparently not studied. However, based on the well-known data they should also regulate the activity of the OXTR gene. Together, methylase and acetylases form a complex. This complex can a priori inhibit or activate OXTR genes. They should participate in the reprogramming in each particular group of OXTR cells as a local mechanism in hierarchy of the groups of OXTR cells.

Epigenetic regulation, known as the chromatin remodeling in neurons, describes a process in which the activity of particular gene controlled by chromatin structure near this gene. Remodeling of chromatin includes several covalent modifications of histone (for example, acetylation, phosphorylation and methylation). It also includes the activity of ATPases containing protein complexes that move histone oligomers along of DNA strands, DNA methylation and binding various transcription factors, transcriptional coactivation and corepressors. They all operate in coordination, defining the activity of this gene. Numerous investigations were conducted in this area; however they are beyond of the scope of this study. Let’s only note that the difficult problem is exactly the coordination patterns of factors of epigenetic gene regulation in each particular case. This fully applies to the OXTR gene.

We proceed from the assumption that the basis for adaptation (plasticity) to the changed social environment obviously is switching from one OXTR-complex of cells on the other. Proceeding from the foregoing, it is possible to put forward a hypothesis that explains extremes of human social behavior.

Plasticity hypothesis does not explain the appearance of personalities, completely resistant to social reprogramming with an insurmountable obstacle to the action of plasticity. The most pure form of it is righteous of the World. One of the examples can be such personality as Irena Sandler. Persistent and long-lasting resistance to adapt to the new environment when someone fully understands inevitability of his own death is an extreme. The personality may have a block in switching from one to the other OXTR complexes of cells. In other words, the reason may be in genetically inherited properties of the entire hierarchy of the OXTR cells complexes.

An important question set in the beginning is about a division of any population into three groups. It formally received a positive resolution: two alleles of OXTR gene divide the population into three groups, although functionally there are two groups. Quite a meaningful solution, however, can only be achieved after a similar analysis of the relevant data on the two genes of vasopressin receptors.

A scheme (hypothesis) that can be formulated only in the presence of data on all three genes, looks like this. Reprogramming of heterozygous individual occurs as a result of switching to other OXTR-V1a and V1b complexes of cells with a different activity ratio of alleles of genes, but actually without changing alleles themselves. Homozygous persons are subject to the same patterns, i.e. a change of their social behavior between the two extreme values is possible. The extreme values for the OXTR gene are prosocial and asocial behavior. Antisocial behavior of GG-OXTR-individuals is not described.

Conclusion

In the brain neurons form (morpho-?) functional groups with OXTR. OXTR cells due to their connections are prepared for implementing different behavioral modes of an individual. The switch from one OXTR group cells to another occurs when macroenvironment of individual is changed. When social reprogramming of an individual occurs, switching should be accompanied by promoter demethylation and histone acetylation in the gene promoter area of the new commencing group of OXTR cells. This enables transcription. The specific path from external irritants with the subsequent processing of information in the brain and transfer orders for switching processes, demethylation and acetylation of OXTR gene promoter region in certain cells is still unknown. An environment is the source of the signals, acquiring through the senses and delivered to the brain. The signals are subjected to adequate processing in the human brain and the resulting activity comes to certain cells with activating oxytocin receptor through synapses. I.e. decision, in which certain groups of cells OXTR gene must be activated takes the brain. Selection of new groups of cells with OXTR gene and subsequent gene activation takes place. The data described in the investigation conducted by Chika Kusui et al. (2001) can serve as a model of this process. HepG2 derived from human hepatoblastoma, in which OTR gene transcription was suppressed was treated with a demethylating agent, 5-azacytidine (Aza-C) for 2 days. Semi quantitative RT-PCR indicated that OTR mRNA was significantly increased by Aza-C treatment in a dose-dependent manner (see also Silvia Ripamonti et al (2017). Indirect argument in favor of close connection with OXTR gene and synapses is a fact described by these authors. They report: "We detected an increased number of excitatory synapses in Oxtr−/−cultures as compared to Oxtr+/+ cultures». The process of switching includes activation of a new group of OXTR cells via promoter demethylation and histone acetylation of the OXTR gene promoter. However, it is still unknown how the signal pathway from OXTR cell synapses to acetylases and methylases near OXTR gene promoter works. In general, it is a much more complex process and object than one which C. Meaney group deals with. However, on a more complex object more simple explanation of adequacy of epigenetic constituent in the chain of processes to the signals from the environment is possible. The accuracy and adequacy of the response of OXTR structures is still provided by analytical work of brain compartments. The answer to the main question how synapses of the brain cells initiate methylation-demethylation, acetylation-deacetylation of OXTR genes in the new group of OXTR cells at the final stage is pending. In the brain, we are dealing with a hierarchy of groups of OXTR cells that provides different options of social behavior of an individual depending on the environment. In each such group the epigenetic mechanism of methylation and acetylation regulates the OXTR gene expression.

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