REWARD PATHWAY – THE COURSE
FROM SUBSTANCE ABUSE TO ADDICTION.

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Abstract.

It is well-known that drug use leads to the person’s addiction enclosing him in the fake microcosm of the substances. From the first trial use to the physical dependence stage, the person is following a specific path to the fatal. In this article, an approach of this path is attempted in the light of both the molecular mechanisms and the subsequent changes in the cellular metabolism occurring by the first use, resulting in permanent lesions of specific neural circuits.

1. Introduction.

The reward pathway is essentially a specific neural circuit, the stimulation of which causes pleasant emotions of satisfaction to the person [1]. Its physical function is to promote the basic biological goals of both survival and reproduction and it belongs to the oldest neural pathways in the evolutionary path of the species [2]. It has been mapped accurately, by the intracranial self-stimulation (ICSS) technique in the laboratory animals. Starting from the
ventral tegmental area (VTA), it is connected with the limbic system nuclei and it reaches the prefrontal lobe (fig. 1).

Fig. 1
Reward pathway.

The information is transferred from the ventral tegmental area (VTA) to the nucleus accumbens and it reaches the prefrontal lobe.

(translated and processed).

Neurotransmitter of the reward pathway is dopamine. VTA dopaminergic neurons are ending in the nucleus accumbens (NAc) and the prefrontal lobe [3-4]. The other limbic system nuclei (amygdala, hippocampus, etc.) are connected with this pathway and they have their own role in the complex function concerning both motivation and reward [5].

In this crucial pathway drugs are acting. The arrogation, the alien and imprudent activation of the reward pathway at its normal function expense, lead the person to the abuse sensitization and then to the addiction compulsion.

The strong activation of the reward pathway by the drugs, results in becoming insufficient for the physical stimulus to mobilize this neural circuit. Thus, the user is seeking for the satisfaction emotions through substance abuse [6]. The drug-seeking desire is due to
cellular function changes caused by the mobilization and gene expression. It is important to be stressed that these changes at a gene level, are starting immediately by the use and they lead to addiction through changes of the synaptic surfaces.

2. **Molecular and genetic basis of the addiction.**

The drugs action causes activation of many synapses of the same dendrite axis. The increased calcium intake and the increased calcium release from the endoplasmic reticulum, the CaM-KII activation and the cAMP formation through the adenylyl cyclase action [7], lead to the PKA (protein kinase) activation resulting in a change of the cell phosphorylation state. cAMP has a synapto-nuclear messenger effect and being transferred to the nucleus it triggers both the transcription and the translation of specific genes known as immediate early genes – IEGs–. This occurs through the cAMP binding with a specific binding protein (cAMP-responsive element binding proteins or CREBP). These proteins are located in the IEGs regulatory regions and their binding with cAMP causes their configuration change, detach from the binding site on DNA and onset of the transcription. Genes with IEGs characteristics was found to be zif-268 as c-fos and c-jun genes families [8-9-10-11].

Changes in the gene expression in the adult brain by the drugs action seems to be due to the transcription factors (cAMP) regulation [12-13]. The altered expression of the genes – targets results to the creation of additional post-transcriptional factors and the subsequent protein synthesis [14] may give rise to ionic channels, receptors, structural and cytoskeletal molecules leading to relatively stable changes of the synaptic surfaces in the form of either long-term potentiation (LTP) or long-term depression (LTD).

The change of the cell phosphorylation state, the activation of the transcriptional and the post-transcriptional factors creation are the molecular mechanisms leading the user to seek
for the drug incitement to the pursuit for rewarding stimuli. On resumption, the cell will be driven to the longer-lived post-transcriptional factors creation affecting the cell metabolism for a long time, even if it is not under the drugs action [15-16]. Thus, the abuser switches from the "want" to the addiction compulsion.

The main post-transcriptional factor with a lifetime of 6-8 weeks which was found in the addicted individuals neurons is Δ-fosB protein [17-18]. This protein, in addition to its stability, is involved in the formation of another protein-activator, AP-1. It is a dimer composed of Δ-fosB and a jun family protein. It is particularly stable, and it activates the transcription by acting in a particular DNA sequence [19-20]. A persistent AP-1 activity was found in the addicts neurons, even for a period of years since the drug abuse withdrawing.

Changes in gene expression may be permanent when occurring through permanent changes in the nucleosomes structure. Such changes occur normally during organogenesis and cellular differentiation only. Chronic drug abuse was found to cause changes in the histones surrounding the genes [21], resulting in the long-term regulation of the target genes. The histones modifications persist for a long time and they are involved in producing neurotrophic factors which are necessary for the permanent changes establishing in the nervous system. This remains to date as the oldest example of chromatin remodeling in the brain after chronic drug abuse [22].

The transcription mechanisms action creates the molecular adaptations reducing the individual sensitivity to the reward effects of the subsequent exposures to drugs (tolerance) and declining the reward pathway (dependence) [23-24]. Thus the person is driven to a loss of control and drug use escalation. The permanent alterations in the synaptic membranes [25-26] and the alteration of the dendritic spines structure comprise the very long-term alterations in both structure and functioning of the brain underling the addiction.
References

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