Commentary: Addiction as an adaptation process in the brain, a view from neurobiology

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Abstract

Research on the brain mechanisms of dependence on alcohol and drugs of abuse has rapidly advanced during the last two decades. We know the main processes, especially how the drugs are acting on their targets on brain cells, but this basic knowledge has not been well translated to better therapies. Not surprisingly, neurobiological addiction research is tackling the same fundamental questions as all neuropsychiatric research. For example, what are the roles of individual neuronal populations in different phases of addiction (development, maintenance, craving and compulsion, abstinence and relapse)? For preclinical research, novel neurogenetic methods now show great promise to answer at least some of the questions, but more innovative work is required to build models and find mechanisms for social and environmental interactions in addiction and to translate the inventions to clinical therapies. Addiction as a disease concept still gives a proper framework for this line of important research.

The term "addiction" is often used in medical writings. Just typing the word in the search field of the PubMed database generates over 40,000 references to the term, the first one dating back to more than 100 years ago (1914). This enormous usage of the term makes one feel humble, although everybody knows that the word/concept has been/is used in various meanings at different times and by different scientists and politicians.

Neurobiology describes drug addiction as a persistent adaptation process to repeated (voluntary) consumption of addictive substances (Figure 1). Therefore, neurobiology can conveniently dissect the process of addiction into subcomponents to be more precisely studied separately. The well-known problem in biomedical sciences on animal models of human diseases is that the experiments that would be most relevant to human conditions lack the precision, especially at the brain cellular and molecular levels (except perhaps for genetic polymorphisms). For example, activation of various brain circuits and neurons can be monitored precisely in neurobiological models, but human brain imaging systems allows only brain regional measurements. Thus, if neurobiology would only study the addicted human brain, we would know very little how the drugs are working and how the brain is adapting to their repeated presence and withdrawal. We would also know little of the mechanisms of how drug consumption develops into habits and compulsive behavior. Since addiction has been related to the fundamental processes of the brain, such as learning and memory, the research in recent years has deta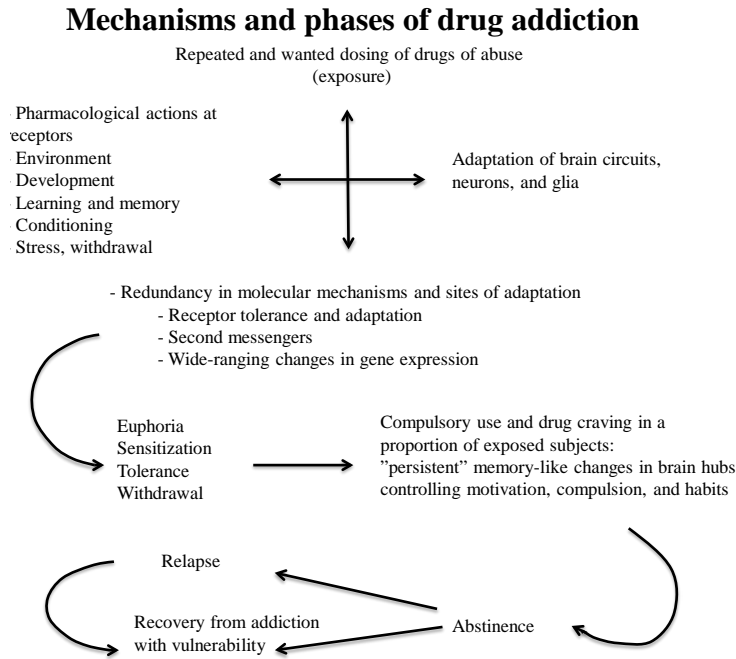iled the mechanisms of many addictive drugs in regulating the addiction-related pathways of the rodent brain (Kauer & Malenka, 2007; Luscher & Ungless, 2006).

One important aspect in brain research and biology in general has been the understanding that there are redundant processes that operate at neuronal circuitry and molecular levels. For example, alcohol-related behavioral effects and chronic abuse-related behaviors can be explained by multiple primary molecular actions of small hydrophilic ethanol molecules that are distributed throughout the body water space (Spanagel, 2009). Alcohol can relieve anxiety in rodent models by enhancing inhibitory GABA mechanisms, by reducing excitatory glutamate mechanisms, or by enhancing neuropeptide mechanisms, such as neuropeptide Y (NPY) and opioid peptides, with each component also showing a strong effect alone. Maybe these different processes can at some point be effectively related to subtypes of alcoholism? What we know much more poorly is how the voluntary self-administration (oral or operant intravenous consumption) is transformed into compulsive drug taking, but the current evidence suggests that there must also be multiple pathways into compulsion and relapse (Everitt & Robbins, 2005).

Why is the term addiction beneficial for biomedical scientists? There are two points that I want to make here. First, the addiction field as its own entity is a way of separating a small "discipline" for the scientists that are interested in understanding the disease of addiction and making a genuine effort in solving scientific questions related to the field. Second, as a respected separate field of

Figure 1

Flow chart of the mechanisms of drug addiction, based on concepts nowadays accepted in pharmacology textbooks.

Mechanisms and phases of drug addiction

Repeated and wanted dosing of drugs of abuse
(exposure)

· Pharmacological actions at
  receptors
· Environment
· Development
· Learning and memory
· Conditioning
· Stress, withdrawal

Adaptation of brain circuits,
neurons, and glia

- Redundancy in molecular mechanisms and sites of adaptation
  - Receptor tolerance and adaptation
  - Second messengers
  - Wide-ranging changes in gene expression

Euphoria
Sensitization
Tolerance
Withdrawal

Compulsory use and drug craving in a
proportion of exposed subjects:
"persistent" memory-like changes in brain hubs
controlling motivation, compulsion, and habits

Relapse

Recovery from addiction
with vulnerability

Abstinence

science, the funding most likely is better than if all biomedical addiction research would be distributed to parts of pharmacology, toxicology, neuroscience, or psychiatry. On the other hand, it has to be admitted that any advancement in the addiction field is based strongly on the general advancement of biomedical and biological sciences in methodology and concepts.

Emerging new concepts and results from selective modulation of single neuronal populations and from functional and molecular modulation of synaptic memory processes are two promising new areas of neurobiological addiction research. For example, we can regulate reward/ aversion by selective activation/inactivation of midbrain dopamine neurons or inhibitory GABA neurons (Adamantidis et al., 2011; Tan et al., 2012; van Zessen, Phillips, Budygin, & Stuber, 2012) using novel optogenetic or pharmacogenetic tools that have given for the first time the possibility to modulate brain activity at a single neuronal population level. These new methods are based on genetic modification of specific neuronal populations, often using viral vectors in the transfer of light or drug-sensitive ion channels/receptors that can be activated later to stimulate or inhibit neuronal firing without disturbing the basic functions of the brain (Deisseroth & Schnitzer, 2013; Wulff et al., 2007). While this kind of detailed basic neurobiological research is still out of reach in human addiction research, more selective tools are also emerging for human research and treatment. It is interesting that an old method of brain electrical stimulation is intensively studied at present, fine-tuned and tried for the treatment of alcohol addiction (Heinze et al., 2009; Kuhn et al., 2011;

Pierce & Vassoler, 2013), based on basic research and on human brain imaging research. A very specific kind of reward pathway activation has been shown to induce remarkable reduction in alcohol drinking of rats (Bass et al., 2013), suggesting that modulation of neuronal activity in the addicted brain in a minor but very precise fashion can have efficacy. So, goal-directed and habitual behaviors can be modulated. But again, these novel tools and ideas are useful not only for addiction research but are also relevant to most other neuropsychiatric illnesses, such as depression and anxiety.

Memory traces are thought to be permanent in a healthy brain. However, recent exciting findings of erasure of memory traces by a selective antagonist of the protein kinase M zeta (Li et al., 2011; Sacktor, 2011; Shema, Sacktor, & Dudai, 2007) have increased the hope that permanently established neuronal connections could be reorganized later in life. Although these results have been questioned (Lisman, 2011; Volk, Bachman, Johnson, Yu, & Huganir, 2013; Wu-Zhang, Schramm, Nabavi, Malinow, & Newton, 2012), indicating that we do not understand the molecular mechanisms well enough, this line of research might turn out to be very fruitful for the future understanding of the memory-like processes that make compulsive addiction so persistent. How do "addicted" synapses differ from other synapses? Are they located differently in neurons or do they contain proteins or other molecules that could be selectively targeted for inactivation during the treatment process? Can these synapses be programmed in early development by adverse life events,

and once identified can they be inactivated by specific therapies?

Synaptic strength is modulated by neuronal activity and drugs of abuse (Citri & Malenka, 2008), which can be mimicked by optogenetic methods at desired neuronal populations. So, certain kinds of neurostimulation can activate and strengthen synaptic connections, while another kind can depress and weaken them (Nabavi et al., 2014). Could we highjack the compulsive motivational processes harnessed by addictive drugs back to motivational tasks for non-addictive behaviors? Basic research has suggested that once these processes are activated by one drug, the effects of other drugs or other rewarding stimuli are occluded (Borgland, Malenka, & Bonci, 2004; Chen et al., 2008; Wise & Koob, 2014), suggesting that there is a ceiling effect in how much neuroplasticity, neurodegeneration, and brain modulation various drugs can induce.

Let us hope that it does not take another 100 years before we know how to self-prevent the development of addiction to harmful substances and habits and before physicians know how to effectively cure the addicted patient once some kind of compulsive addictive behavior has emerged. In the meantime, the addiction concept will inevitably be revised, transformed, or renamed as relevant processes are better established in the human brain to orchestrate emotional, motivational, and behavioral options within a native environment.

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