Depression, Addiction and the Brain Reward System

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The brain reward system consists of the fundamental neural pathways involved in eliciting motivation and rewarding experiences. This neural network shares striking neurochemical and morphological similarities among different species. Impaired function of the brain reward system is implicated in both depressive behavior and drug addiction, and comorbidity between these two states in humans has been statistically documented.

Our main goal is the study of mechanisms by which the brain reward system affects mood and motivation, and the development of new tools to examine and affect neuronal processes at the root of depressive behavior and drug addiction. We use animal models for addiction and depressive behavior to study neurochemical and electrophysiological alterations in their brain reward system and we study the effect of repeated electrical stimulation of specific reward-related brain sites on both behavioral, neurochemical and electrophysiological outcomes.

In our addiction model, animals learn to press a lever to self-administer heroin or cocaine directly to an implanted intravenous catheter. We found that repeated cocaine use induces long-term alterations in levels of glutamatergic receptors within subregions of the ventral tegmental area and the nucleus accumbens, which are fundamental sites in the brain reward system. These long-lasting alterations can be viewed as expression of brain plasticity induced by chronic drug use. Repeated subconvulsive electrical stimulation of either a major reward pathway in the lateral hypothalamus or in the prefrontal cortex resulted in partial normalization of these glutamatergic alterations and induced a reduction in drug seeking behavior as measured by the frequency of lever presses. On the other hand, our localized electrical stimulation treatment did not impair locomotion as measured in exploration boxes or learning and memory as measured in a water maze paradigm.

Our models for depression involve a battery of standard behavioral tests for motivation, hedonia and exploration. Depression has both genetic and ‘environmental’ components. In order to study the genetic components we are developing an animal model based on selective breeding for depressive, normal or motivated behaviors as measured by a battery of automated behavioral tests. We are now testing the 7th generation and so far we found most aspects of motivation and hedonia to be hereditary in our model. Gene expression in tissue punches of reward-related brain regions will be measured in the next generation. A key factor in the ‘environmental’ component of depression is chronic stress. Exposure to chronic mild stress (CMS) is known to induce anhedonia in adult animals, and is associated with the development of depression in humans. However, the behavioral effects of CMS in young animals have not been previously characterized, and little is known about the long-term neurochemical effects of CMS in either young or adult animals. A growing body of data suggests that brain-derived neurotrophic factor (BDNF) and the glutamatergic system, which are known to play a major role in neuronal plasticity, may be involved in the pathophysiology and treatment of mood disorders. We found that CMS induced anhedonia in adult but not in young animals, as measured by a battery of behavioral paradigms. Furthermore, while CMS decreased BDNF levels in the hippocampus of adult rats, it increased BDNF levels in young rats. We also found that CMS altered AMPA receptor GluR1 subunit levels in the hippocampus and the nucleus accumbens of adult, but not young rats. Therefore, chronic stress exerts substantially different neurochemical effects in young and adult animals that may explain our finding on the behavioral resilience of young animals to chronic stress. Further research on the link between BDNF and AMPA and their role in the pathophysiology of depression may help in establishing novel therapeutics for the treatment of stress-induced depressive behavior. Nevertheless, our research support the argument that adolescent depression is different from adult depression in its pathophysiology and therefore in its treatment strategies.
As we found with our cocaine addiction study, subconvulsive electrical stimulation of specific reward-related brain regions appear effective in normalizing depressive behaviors induced by CMS as well as BDNF levels in the hippocampus of adult CMS animals.

In order to further examine plasticity related alterations in the function of the brain reward system that are critically involved in depressive behavior and drug addiction, we are using in-vivo electrophysiological recording. Specifically, we examine modifications in the ventral subiculum-nucleus accumbens (vSub-NAC) pathway, which is implicated in processing of contextual information and motivational function. We recorded evoked potentials in the NAC in response to stimulation of vSub of the hippocampus in anesthetized animals. Recording from different sub-regions in the NAC of the naive rat revealed a non-homogeneous spread of responses: (a) a source at the dorso-lateral shell, (b) a sink at the ventro-medial shell and (c) no response in the NAC core. Therefore, the vSub innervate the NAC non-homogeneously. This patterned input suggests that the same information coming from the hippocampus can be subjected to different processing within the NAC. In response to paired-pulse stimulation and high frequency stimulation protocols, the vSub-NAC pathway demonstrated short-term plasticity. However, this pathway in naive rats was not amenable to long-term potentiation (LTP). Surprisingly, LTP was induced following recovery from an acute cocaine injection but not following a saline injection. This suggests that a single cocaine exposure induces long-term metaplasticity in this pathway.

We further examined alterations in this pathway in animals subjected to chronic mild stress. Exposure to CMS induced depressive behaviors such as anhedonia (e.g. reduced preference for a sweet solution) and a reduction in BDNF levels in both the vSub and the NAC. Electrophysiological recording revealed abnormalities in the vSub-NAC pathway of animals exposed to CMS. The most striking observation was that LTP was induced in this pathway only in animals exposed to CMS but not in the normal controls. As this pathway process environmental inputs to the reward system, our findings may indicate how exposure to chronic stress induces long-lasting susceptibility to environmental inputs.

In parallel, and based on some results obtained in the abovementioned projects, we have started to test the efficacy of repeated stimulation of reward-related regions of the human brain in treating depressive disorders and addiction. These studies are done in collaboration with clinical centers. We have previously developed a novel coil for non-invasive transcranial magnetic stimulation of reward-related regions in the human brain and proved the ability of our approach to stimulate deep brain regions non-invasively and safely. These studies will further enrich our knowledge of brain reward pathways and will be of paramount importance in designing novel treatments for depression and addiction.

Selected publications

Acknowledgements
The National Institute for Psychobiology; Abish-Frankel Foundation; The BIAL foundation. A.Z. is an incumbent of the Joseph and Celia Reskin Career Development Chair. Benoziyo Center for Neurological Disease; The Rosenzweig-Coopersmith Foundation; Gerhard & Hannah Bacharach Fund; Yeda.