ELSEVIER

FIELD EDITOR EDITORIAL

The Future of Neurophysiology in Neuropsychopharmacology

Information processing in the brain occurs primarily by electrical impulses in neurons that release neurotransmitters and influence the electrical activity of other neurons. This function is regulated by a variety of factors, and is the primary target of drugs aimed at treating mental dysfunctions. Thus, the study of electrical activity in neurons (neurophysiology) is at the heart of how the brain processes information and how drugs influence mental functioning, and is central to neuropsychopharmacology.

The importance of neurophysiology in neuropsychopharmacology is confirmed with the reorganization of this Journal, and the creation of a separate field of neurophysiology for the review of submitted manuscripts. In this editorial, I emphasize the importance of neurophysiology to neuropsychopharmacology now and in the future. Compared to the role that it plays, and will play, in neuropsychopharmacology, neurophysiology has been under-represented in this journal. A major goal of mine is to publish greater numbers of outstanding neurophysiology articles in *Neuropsychopharmacology.*

There are several aspects of neurophysiology that stand out as having substantial promise for neuropsychopharmacology in the future. These span the neurophysiology spectrum, from molecular neurophysiology to behavioral and cognitive neurophysiology. As pointed out below, integration among these fields is a growing, and increasingly powerful, aspect of neurophysiology.

MOLECULAR NEUROPHYSIOLOGY

This is an area that is developing rapidly, and has already made substantial contributions to our field. Patch clamp analysis of currents through single channels, a technique for which Sakmann and Neher won the Nobel Prize, is an extremely powerful method to analyze neurophysiological function at the molecular level. Using this methodology, one can easily test the effects of minute manipulations of the molecular structure of receptors and their associated channels, as well as the individual subunits of G proteins and second messenger systems. One can determine exactly at what amino acids in the protein of the channel molecule or subunit an antagonist or drug acts, or at what point protein phosphorylation modulates receptor function. Such combined molecular biology and neurophysiology allows for the first time a definitive connection between structure and function at the molecular level. The upshot of this for neuropsychopharmacology is that such an understanding will allow (i) a more detailed understanding of the functional basis of genetically linked disorders of brain function, and (ii) the rational development of more effective and selective pharmacological agents and therapeutic drugs. For example, understanding what part of the NMDA receptor-channel complex is affected by alcohol could lead to the development of a drug to blunt alcohol antagonism of NMDA receptor function, thought to be responsible for many aspects of alcohol intoxication. It should also be noted that these neurophysiological methods are readily applicable to human samples (e.g., slices or cultures from biopsies) so that functional data for single molecules (e.g., channels) can be compared for tissue from normal and diseased brains.

CELLULAR NEUROPHYSIOLOGY

Although the neurophysiological analysis of single molecules is an important avenue for understanding the molecular and genetic bases of mental disorders,

NEUROPSYCHOPHARMACOLOGY 1999–VOL. 20, NO. 5

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/99/$–see front matter
PII S0893-133X(99)00013-5

such findings must be integrated into a cellular-level analysis to understand how channel, receptor, and messenger molecules influence information processing in the nervous system. No single channel operates alone in determining the impulse activity of a neuron; instead, each neuron integrates thousands of synaptic inputs, and even greater numbers of ion channels, in determining cellular membrane potential. The functional significance of the ever advancing insights into diffusable intracellular 2nd messenger molecules can be very profitably studied by intracellular or whole-cell patch clamp analysis in cultured neurons or brain slices. Current and future work using such cellular neurophysiology in slices and cultures from animals with specific genetic manipulations of specific molecules (via, e.g., transgenic or knockout techniques) will be critical to understand the importance of such manipulations for the function of specific brain neurons. These approaches are also critical to drug development. For example, the design of neuroleptics that interfere with a particular subset of dopamine or serotonin receptors on identified cortical neurons is now a feasible undertaking with slice or culture neurophysiology.

Electrotonic coupling is an aspect of cellular neurophysiology that is not considered frequently in neuropsychopharmacology. This communication via gap junction channels formed by connexin proteins in neuronal membranes is known to be common during development. It is believed that in the mature CNS electrotonic coupling exists in only a few specialized areas such as retina and inferior olive. However, increasing evidence indicates that such coupling may be much more widespread than originally believed. Neurons appear to be electrotonically coupled in the adult caudate and nucleus accumbens, as well as in noradrenergic neurons of the locus coeruleus and dopaminergic cells of the substantia nigra. Notably, this coupling is flexible, and can appear or vanish with changes in neurotransmitter inputs and 2nd messenger molecules. This raises the possibility that electrotonic coupling may be targeted in a selective manner by drugs. The ability of electrotonic coupling to synchronize activity among neurons, and the powerful effects of neuronal synchronization on information processing in the brain, indicates that the pharmacology of electrotonic coupling is an important area of investigation for neuropsychopharmacology in the future.

SYSTEMS NEUROPHYSIOLOGY

Just as the influences of individual molecules must be integrated to understand their functional significance at a cellular level, the operations of individual neurons must be integrated into circuits and networks to understand how such activity influences other brain areas, and ultimately contribute to a psychological or behavioral function. Many studies at this level that are important for neuropsychopharmacology involve extracellular recording of impulse activity from neurons in a particular brain area in response to drug administration in anesthetized animals. Studies using local drug administration are important for determining the site of drug effects where inputs that may be severed in the slice remain intact. Studies using systemic drug administration lack information about locus of action, but are important nonetheless to determine how the drug affects specific neurons when given in a clinically relevant dose and manner. Investigations in brain slices often lose sight of the fact that neuronal properties can be substantially altered in the process of obtaining the slice (truncation of dendrites, loss of synaptic inputs, loss of circulating factors, etc.). Therefore, analyses of drug actions using intracellular recordings in the intact animal is an important (more physiologically relevant) extension of similar studies in brain slices that deserves more attention in the future. Recent advances in multichannel electrode recording, as well as optical imaging methods for cortical as well as subcortical structures in the intact animal, offer exciting new approaches to study the activities of populations and networks of neurons in the intact animal.

BEHAVIORAL NEUROPHYSIOLOGY

This is the ultimate level of integration in neurophysiology. These studies specify the behavioral significance of neurophysiological properties of single molecules, individual neurons, and circuits and networks of neurons. This level of analysis employs single neuron recording in animals, or slow-wave recording in humans, and is critical for studying brain mechanisms of complex behaviors and cognitive processes. While molecular and cellular experiments are important for understanding details of processes involved in mental dysfunction or drug responses, they are unable to integrate such results to ultimately and completely explain cognitive functions such as attention, perception, emotion, or memory. An analogous relationship exists between physics and chemistry: While the principles of physics are critical to our understanding of chemistry, they are not sufficient to fully predict or understand the properties of chemical reactions. It is fundamentally necessary to conduct experiments in chemistry per se or, as is the case at hand, in behavioral neurophysiology.

Although the behavioral functions of brain areas can also be examined with lesions, there are several problems inherent with many such approaches (plasticity, recovery of function, etc.). Recordings in animals per-

forming a behavioral task allow a less invasive analysis of the behavioral role of neurons. If the neurons in question are involved in a particular behavior, then their activity should vary with that behavior in a predictable manner. More often than not, recordings detail much more about possible neural involvement in a specific behavioral or cognitive process than originally imagined. This is important, as such observations are an important source for hypotheses about the behavioral functions of brain areas, which can then be elaborated with computational modeling approaches, and tested with manipulations of the neurons in question (described below).

Computational modeling has traditionally been applied to cellular analyses of neurophysiological function using biologically realistic models. However, there is a great deal to be gained from the iterative interaction between modeling and neurophysiology at the behavioral level as well. One approach that has great promise for the future is the use of hybrid models, composed of a biologically realistic component to capture the neurons being recorded plus a more abstract connectionist component to represent the behavior performed during the recordings. Such models are a powerful means to make hypotheses about the behavioral functions of neurons more specific and testable.

Microinjections into brain areas of behaving animals are an excellent alternative to lesions for testing hypotheses about the behavioral function of a brain area. This approach can be combined with neurophysiology, so that the activity of neurons can be monitored from an electrode adjacent to a cannula injecting, for example, an inhibitory agent. This produces an immediate, transient "lesion" that is not subject to the confounds of permanent lesions, and also gives a temporal index of the change in activity of the cells in question to correlate with the behavior of the animal. If specific neurons discharge in relation to the behavior, and manipulations of those neurons by local chemical means produce cognitive or behavioral changes that are consistent with the recordings, strong evidence is obtained in favor of the behavioral role for these neurons. Such local microinjection/recording techniques in behaving animals can also be used to test the sites of action of drugs for specific behavioral effects.

Another area of substantial potential here is the use of multiple electrodes to simultaneously record activities of several individual neurons during behavioral experiments. Studies of this type are important as they extend the analysis of single neurons to networks of neurons. It is, of course, networks of cells, not individual neurons, which underlie complex behavior.

In addition, very little work at the interface of neurophysiology and in neuropharmacology has been done in behaving animals. Clearly, it is important to investigate the neurophysiology of drug actions in unanesthetized animals, as anesthesia may have profound effects on drug responses of neurons. One area that is only little studied is the activity of individual brain neurons in animals self-administering drugs, or in other types of drug abuse studies. A particularly large gap exists in this regard concerning the cognitive effects of abused drugs. Certainly addiction involves important changes in attention, memory, and other high-level cognitive processes. These processes cannot be understood with molecular or cellular studies of the effects of addictive drugs alone. Studies of the effects of addictive drugs on target neurons in, e.g., behaving primates performing cognitive tasks that tap into changes associated with addiction, will provide exciting new views on brain substrates of addiction.

A final point that is noteworthy here is that behavioral neurophysiology is critical for a *mechanistic* understanding of cognitive processes studied with functional imaging techniques. A danger in imaging studies (e.g., PET or fMRI) is that scanned images of, e.g., increased activity in area X during task Y may be interpreted to mean that area X mediates a function presumably tapped by task Y. This thinking resembles phrenology of many years ago. Lost in this equation is the fact that area X transforms the signals it receives, before passing them on elsewhere. These signals are transmitted and transformed at the cellular level, via electrical and neurochemical signaling. The real function of area X is not the global behavioral or mental process targeted by the task, but rather the transformation of the signals fed through X, and on to X's targets. Thus, whereas scanning denotes areas that may be involved in particular behaviors and processes, behavioral neurophysiology is required to elucidate the functions of those areas and the underlying mechanisms.

In addition to these neuronal analyses in behavioral neurophysiology, new approaches in ERP and EEG recordings have substantial promise. Investigators are learning a great deal about the progression of signal processing, and the localization of such processing to specific brain areas, by the use of large numbers of scalp electrodes in humans. Such studies offer a great deal of promise in conjuction with fMRI and other functional imaging. The spatial accuracy and resolution of imaging techniques complements the temporal resolution of ERP methods, so that studies in intact humans can be performed with much substantial spatial and temporal resolution.

In conclusion, neurophysiology is critical for the future of neuropsychopharmacology. Neuropsychopharmacology is dependent upon neurophysiology for mechanistic understanding of mental function and dysfunction, and of drug actions in brain and behavior. This mechanistic knowledge is also important for the development of better pharmacologic tools. Given the central importance of neurophysiology to neuropsychopharmacology, I believe that neurophysiology is un-

der-represented in this journal. As the new field editor for neurophysiology, I hope to change this situation. *Neuropsychopharmacology* is the logical vehicle for communicating new insights in neurophysiology to basic and clinical scientists in this field. Neurophysiology articles in all of the areas discussed above are of high relevance to neuropsychopharmacology, and high quality manuscripts in these areas are encouraged to provide the most current and important studies to our field.

Gary Aston-Jones, Ph.D.
Department of Psychiatry
University of Pennsylvania School of Medicine
Philadelphia, PA