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Review

Central Nervous System and its Disease Models on a Chip

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Technologies for microfluidics and biological microelectromechanical systems have been rapidly progressing over the past decade, enabling the development of unique microplatforms for *in vitro* human central nervous system (CNS) and related disease models. Most fundamental techniques include manipulation of axons, synapses, and neuronal networks, and different culture conditions are possible, such as compartmental, co-culturing, and 3D. Various CNS disease models, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), epilepsy, *N*-methyl-D-aspartate receptor (NMDAR) encephalitis, migraine, diffuse axonal injury, and neuronal migration disorders, have been successfully established on microplatforms. In this review, we summarize fundamental technologies and current existing CNS disease models on microplatforms. We also discuss possible future directions, including application of these methods to pathological studies, drug screening, and personalized medicine, with 3D and personalized disease models that could generate more realistic CNS disease models.

Trends

Various microplatforms mimicking *in vivo* microenvironments of central nervous system (CNS) are reviewed.

In vitro CNS disease models, including Alzheimer's disease, Parkinson's disease, and so on, using microplatforms are introduced.

Future directions of *in vitro* CNS disease model based on microplatforms are described, including its application to pathology studies, drug screening, and personalized medicine.

In Vitro Models of the CNS

The CNS is highly compartmentalized and layered, containing diverse cell types with plastic connectivity via axon and dendrite outgrowths [1]. Animal-based CNS disease models have been used to study human brain function and related diseases. However, these *in vivo* approaches have various limitations, such as high costs, low-throughput, labor-intensive, and time-consuming processes, and experimental variations. These limitations led neuroscientists to develop simplified and high-throughput *in vitro* CNS disease models. However, the simplicity of *in vitro* tissue models can also lead to biased results and false conclusions. However, these can be reduced by particular technologies that mimic the 3D structure, abundant vasculature, blood–brain barrier (BBB), and cerebrospinal fluid (CSF) of the brain [2]. Organs-on-chips are microengineered platforms that mimic physiological microenvironments and cultured tissues. Until now, the modeled organs-on-chips included the heart, lung, kidney, blood vessels, skin, liver, brain, and pancreas [3,4]. Understanding the mechanisms of CNS functions and causes of diseases also requires systematic platforms capable of mimicking the *in vivo* neuronal environment. Recent progress in microfluidics and microelectromechanical systems (MEMS) has made it possible to develop unique platforms for creating *in vitro* human CNS models that approximate the *in vivo* conditions as far as possible [2]. These technologies have established various *in vitro* CNS disease models of AD, PD, MS, migraine, diffuse axonal injury (DAI), neuronal migration disorders, epilepsy, and NMDAR encephalitis. As shown in Figure 1, the complex *in vivo* environment of the CNS can be established *in vitro* with 2D and 3D neuronal cell cultures on diverse microfluidic platforms, allowing the modeling of critical CNS diseases. The microenvironments and morphology of cells can be controlled by fluidic and patterning technologies. In this review, we identify current fundamental microtechniques that are applicable to the *in vitro* modeling of the CNS and highlight challenges for microplatform-based

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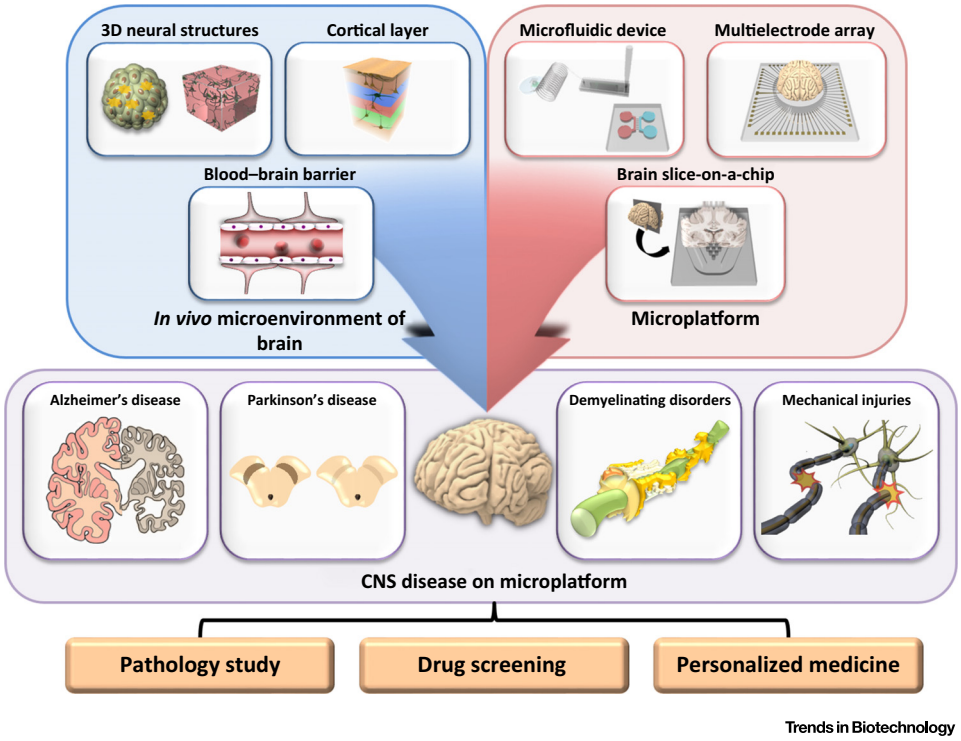

Figure 1. General Conceptions of Central Nervous System (CNS) Disease Models on the Microplatform

CNS disease models in elucidating underlying mechanisms. Finally, we briefly describe the potential technologies applicable to the CNS and CNS disease models and discuss future perspectives.

Fundamental Techniques Dealing with CNS on Microplatforms

In vitro studies of brain pathophysiology have been performed using controlled cultures of neurons, glial cells, and brain tissues on microplatforms designed to mimic the *in vivo* environment of the CNS as closely as possible. These have several advantages, including flexible control of the microenvironment, single-cell handling, real-time analysis, co-culture, compartmentalized culture, perfusion culture, and long-term culture [5]. Such study models can be categorized as axons, co-cultures of neuronal cells, neuronal networks with directionality, brain slices, and reading neuronal activities via microelectrode arrays (MEAs). Table 1 summarizes the currently applicable techniques for CNS models on microplatforms.

Control of CNS Cells on Microplatforms

Microfluidic platforms have been developed with suitable spatial control of neurons by physical channels that restrict the movement of cell bodies and generation of chemical gradients. The CNS comprises neurons, astrocytes, and microglia, and these cells support one another (e.g., glial cells support neuronal survival) and communicate with the extracellular matrix (ECM). To mimic the *in vivo* situation of CNS and its diseases, the control of physical and chemical cues and the proper ratio of these different cell types are important. Using cellular responses to surface topology and chemical modification, one can control desired neuronal constructions by the *in vivo* mimicking of ECM. For the control of surface topology, diverse patterning techniques, including microcontact printing, soft- and photolithography, laser ablation, and so forth, could be used [6]. Surface-modification methods that use polylysine, laminin, polyethylene glycol, and albumin have been extensively used for the control of cell adhesion and growth [6]. Controlling the cell ratio is critical to mimic the *in vivo* environment of diverse CNS diseases; however, the