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Review Article

Neuropharmacology beyond reductionism – A likely prospect

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ABSTRACT

Neuropharmacology had several major past successes, but the last few decades did not witness any leap forward in the drug treatment of brain disorders. Moreover, current drugs used in neurology and psychiatry alleviate the symptoms, while hardly curing any cause of disease, basically because the etiology of most neuro-psychic syndromes is but poorly known. This review argues that this largely derives from the unbalanced prevalence in neuroscience of the analytic reductionist approach, focused on the cellular and molecular level, while the understanding of integrated brain activities remains flimsier. The decline of drug discovery output in the last decades, quite obvious in neuropharmacology, coincided with the advent of the single target-focused search of potent ligands selective for a well-defined protein, deemed critical in a given pathology. However, all the widespread neuro-psychic troubles are multi-mechanistic and polygenic, their complex etiology making unsuited the single-target drug discovery. An evolving approach, based on systems biology considers that a disease expresses a disturbance of the network of interactions underlying organismic functions, rather than alteration of single molecular components. Accordingly, systems pharmacology seeks to restore a disturbed network *via* multi-targeted drugs. This review notices that neuropharmacology in fact relies on drugs which are multi-target, this feature having occurred just because those drugs were selected by phenotypic screening *in vivo*, or emerged from serendipitous clinical observations. The novel systems pharmacology aims, however, to devise *ab initio* multi-target drugs that will appropriately act on multiple molecular entities. Though this is a task much more complex than the single-target strategy, major informatics resources and computational tools for the systemic approach of drug discovery are already set forth and their rapid progress forecasts promising outcomes for neuropharmacology.

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1. Introduction

Neuroscience – the large spectrum of scientific fields that study all the aspects of the nervous system – is currently a most dynamic scientific endeavor in accelerated expansion, largely fueled by the hope that neuroscience progresses might reduce the societal burden of chronic neurological and neuropsychiatric diseases. In fact, the costs linked to those diseases are truly colossal, particularly in the aging post-industrial societies. The worldwide societal costs in 2005 of the dementia alone have been estimated to US$ 315.4 billion, 77% of these occurring in more developed regions of the world. By 2009, the worldwide societal costs of dementia increased by 18% in fixed prices (Wimo et al., 2007, 2010). The past designation by U.S. Congress of the 1990s as the *Decade of the Brain*, with the proclaimed aim "to enhance public awareness of the benefits to be derived from brain research", really increased public and media attention to neuroscience. Advances in describing several brain pathologies have been achieved and remarkable developments in the functional imaging of the brain were indeed realized. However, the hope of radical improvements in the pharmacologic treatment of neurologic and psychiatric disorders did not yet materialize. The modest record of neuropharmacology in the last two decades (see Section 3) is not so surprising consequence of the current limitation of our understanding of the integrated activities of the brain, nonetheless the huge amount of details gathered about its elementary components and processes.

The neurosciences succeeded by now mostly in deepening the analysis and much less in reaching genuine understanding of brain functions, whose complexity derives from the interaction of numerous intricate neuronal circuits operating on a wide range of temporal and spatial scales. In fact, complexity is the very prototypal characteristic of the brain structure and functioning. In view of its number and variety of cells and of their short- and long-range interconnections, the brain is by far the most complex domain of human body, it being commonly thought as the most complex system in the known universe (*e.g.* Singer, 2007). Therefore, brain disorders themselves are complex pathologies from the standpoint of both etiology and symptomatology (*e.g.* Garcia-Cairasco, 2009; Yang and Tsai, 2013).

A marked move toward embracing the complexity, termed *systems biology* (SB), became fully perceptible at the turn of this century in bioscience in general (for general presentations see Bard, 2013; Bizzarri et al., 2013). In basic neuroscience, the rising awareness that the intrinsic complexity of brain functions imposes a systemic approach (Geschwind and Konopka, 2009) can be illustrated by a recent authoritative account of learning and memory in a conceptual framework extending from molecular to systems biology (Kandel et al., 2014). The nascent surpassing of reductionism promises to significantly impact on neuropharmacology, as this review tries to highlight.

2. Cartesian approach: merit and limits

René Descartes' celebrated "*Discours de la méthode*", published in 1637 had an enormous influence on the evolution of all Western science, as it shaped the pattern to optimally advance the knowledge in every domain. In the Part II of that short treatise, Descartes formulated four basic rules that would guide understanding every subject: (i) the rule of evidence ("never to accept anything for true which I did not clearly know to be such"), (ii) the rule of analysis ("divide each of the difficulties under examination into as many parts as possible, and as might be necessary for its adequate solution"), (iii) the rule of synthesis ("commencing with the simplest and easiest to know objects, I might ascend by little and little... to the knowledge of the more complex") and (iv) the rule of completeness ("in every case to make enumerations so complete... that I might be assured that nothing was omitted"). Out of these four, the analytical principle of decomposing the complex matters into their simpler and better understandable components emerged as the cornerstone of the *reductionist approach*, which almost forgot the synthesis (Fig. 1), on the implicit, if not even explicit, assumption that the whole can be understood from the properties of its parts.

2.1. Reductionism *is a major drive to knowledge increase, but it has limits*

The idea that each difficult problem should be divided as much as possible into simpler and easier to apprehend parts, from which should start the understanding before gradually rising to the knowledge of the composed things, had a far-reaching impact on every branch of Western science. Cartesian thinking prompted the mechanics of Newton and climaxed in the classical rational mechanics of late 18th and early 19th centuries. Its impressive success to explain the movements of all bodies, be them terrestrial or cosmic, led to consider as final goal of the study of every phenomenon the unraveling of its *mechanism*. In particular, biology evolved from natural history largely by way of reductionism (Bose, 2013). Firstly, the discoveries about the microscopic organization of plants and animals led in the middle of 19th century to Schleiden's and Schwann's cellular theory. Then, as the organisms are composed of molecules, the biochemistry focused on molecules and biochemical reactions while searching to apprehend organismic phenomena. The pinnacle of the reductionist approach in biology was brought in the second half of 20th century by the impressive achievements of molecular biology (Fang and Casadevall, 2011) that made common the belief that all biology might be explained in terms of chemistry and physics. Similarly, the accumulation of data about brain wiring and its elementary processes led to believe that the mental states and the consciousness might be reduced to the physicochemical reactions in the brain.

The methodological reduction of the explanations to the smallest possible entities brings about the epistemological assumption that the information of a scientific domain about more complex objects of study fully follows from data in scientific domains about simpler objects, so that: biology ← chemistry ← physics. The reductionist physicalism considers that since all matter, both inanimate and living, is built of the same elementary components – atoms, then ultimately elementary particles – everything should obey the same fundamental laws, with the corollary that the only science that studies anything fundamental would be elementary particle physics. This view was brilliantly dismantled decades ago by the Nobel Prize solid-state physicist Philip Anderson. He noticed that reducing everything to fundamental laws does not imply the ability to start from those laws and reconstruct the universe, since at each level of complexity entirely new properties appear, and at each stage entirely new laws, concepts, and generalizations are necessary (Anderson, 1972). While stressing that "Psychology is not applied biology, nor is biology applied chemistry", Anderson deplored that "some molecular biologists [...] try to reduce everything about the human organism to only chemistry, from the common cold and all mental diseases to the religious instinct"(!). Molecular biology has indeed adopted the reductionist attitude to explain biological systems by the physical and chemical properties of their individual components, until biologists and biomedical scientists touched the limits of this approach as it has become evident in various aspects, including a noticeable dwindling of drug discovery in the last decades (see Section 3).

Holistic approaches have been, however, at the core of whole-organism embryology, the debate reductionism *vs.* holism having