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Original article

Neurodegenerative diseases, infectious pathologies and liquid crystals: Hypothesis of a common information vector involving a multidisciplinary approach

Q1 C. Binot [a], C.-H. Chouard [b,*]

[a] Cabinet privé, 12, rue de Terre Neuve, 17410 Saint-Martin-de-Ré, France
[b] Cabinet privé, 10, boulevard Flandrin, 75116 Paris, France

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ABSTRACT

The existence of an information vector common to very different pathologies is the hypothesis of one of us, the argumentation and discussion of which we present here. It is a mesomorphic state of material called liquid crystal. The liquid-ordered (Lo) phase, made up of membrane rafts mediated by cholesterol, lies at the center of our concept. This mesophase is either preexistent and then modified by the pathogenic process, or initiated by the latter. The most notable disorders involved are Alzheimer's, Parkinson's, Charcot and Creutzfeldt–Jakob diseases, flu-like illnesses and acquired immunodeficiency syndrome (AIDS), although this list may well be extended to include other anisotropic, birefringent amyloid proteinopathies, which have properties compatible with those of liquid crystals. Incidentally, numerous conventional infectious pathologies can also induce a mesomorphic state in cell membranes. It has already been established that mesophases contain the chemical information transmitted rom the intramolecular microscopic level, where covalent bonds are applied. Information is then transmitted at the intermolecular macroscopic level, where it is made up of informed, self-organized collections. Electrostatic interactions, coordination of metallic ions, van der Waals forces and donor–acceptor interactions of hydrogen bonding all come into play. These reactions are produced notably in the nanodomains enriched by cholesterol and sphingolipids. Lipids in the cell membrane are where the phase separations favoring elastic hydrodynamic instabilities conducive to the Lo phase take place. In addition, perturbations of the mesomorphic states of membrane rafts due, for example, to lipid dysfunction—even mild ones—with an intracerebral or generalized location could bring about a displacement of thermodynamic equilibrium favoring the initiation and progression of the pathologies under consideration here. Indeed, the most recent work has rendered our hypothesis highly probable. Moreover, our hypothesis is supported by medical and biological observations arising essentially from biophysics and widely documented in

* Corresponding author.
E-mail address: claude@chouard.com (C.-H. Chouard).
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the literature. Thus, these facts expand the number of diagnostic and therapeutic perspectives that could be evoked and perhaps even demand exploration.

1. Introduction

Presented here is our hypothesis that a mesomorphic state called ''liquid crystal'' constitutes an information vector common to various different disorders such as Alzheimer's, Parkinson's, Charcot and Creutzfeldt–Jakob diseases, acquired immunodeficiency syndrome (AIDS) and flu-like illnesses. This hypothesis also includes other anisotropic, birefringent amyloid proteinopathies, which have properties compatible with those of liquid crystal and of numerous infectious diseases due to viruses, bacteria and toxins. In the context of our hypothesis, this information vector contains liquid crystal, made up of membrane rafts mediated by cholesterol, in interaction with neighboring membrane lipids. This mesophase, which is called by some pioneers liquid-ordered (Lo), may be either preexistent and modified by the pathogenic process or initiated by the latter. A lipid dysfunction, either localized to intracerebral membrane rafts or generalized, could be one of the determining factors of the pathogenicity of certain degenerative disorders.

Of the neurodegenerative diseases, Alzheimer's is the deadliest and most costly, despite decades of clinical, epidemiological, genetic and biochemical research that has increased our knowledge of the disease. Yet, there is still no definitive therapy today beyond palliative approaches. A recent update published in the *Journal Nature* [1] emphasized this fact in several articles. For clinicians and biologists, liquid crystals—omnipresent in the world of the living—could constitute a new approach towards the initial processes resulting in numerous different pathologies, and such an essentially multidisciplinary approach is likely to improve the double clinical problem of markers for early diagnosis and effective treatment from the start of certain neurodegenerative disorders. Furthermore, taking mesomorphic states into account would provide essential information on the infectious mechanisms triggered by pathogens that either enter organisms at the level of membrane rafts or generate their own nanodomains.

We estimate that this information vector could be the unifying element that assembles, into a coherent whole, multiple processes that are otherwise apparently unrelated to each other. ''Liquid crystal'', ''mesophase'' and phase Lo' can be considered synonymous terms, with every speciality preferentially using one of them, although they all describe the same state of matter explored by Pierre-Gilles de Gennes. In fact, they constitute a conceptual whole with a logic that makes sense of the diversity of observed signs. Nevertheless, here the term ''liquid crystal'' is used as often as possible.

Our hypothesis is supported by the identification of mesomorphic states associated with neurodegenerative and infectious processes. It is within these plasma and endocellular membranes, particularly at the level of the nanodomains called ''membrane rafts'', that the initial mechanisms leading to the pathologies mentioned above are situated. The amphiphilic lipid bilayer of our cells is a two-dimensional liquid crystal and the Lo phase is made up of membrane rafts [2]. As for the properties common to numerous proteins linked to neurodegenerative diseases, these include tinctorial and optical properties observed within mesomorphic states [3], and birefringent and anisotropic amyloid, proteins that have the peculiarity of being membrane or transmembrane and present within rafts.

Some of these proteins are so-called ''infectious'' and contaminate by proximity, and several membrane proteins, as well as glycosphingolipids, are used as receptors by viruses and other pathogens, including the Aβ peptide. Moreover, it has been discovered that the membrane proteins related to amyloid precursor protein (APP), cellular prion protein PrPC and gp120 protein have a common site of sphingomyelin recognition, thereby underscoring the role of membrane rafts in Alzheimer's and Creutzfeldt–Jakob diseases, and AIDS [4,5].

It is highly likely that the exploration of liquid-crystal states will lead to an understanding of other mechanisms of connective processes of living tissues that are apparently very distant from each other, and it is possible that liquid-crystal states can optimally reflect the complexity of biological systems. Its structure must be sufficiently fluid to allow for diffusion and displacement of molecules, all while conserving an optimal degree of order to carry out selective processes. This double requirement can be filled by a mesomorphic order, but not a purely solid or liquid state.

2. Physical–chemical arguments in favor of a common information vector

It has been established that cholesterol intervenes in a determinant manner in the pathophysiology of numerous neurodegenerative and infectious processes. Essentially, this well-documented fact arises from the medical and biological disciplines, and is related to the following five points derived from physical–chemical experimentation:

- cholesterol plays an essential role [6] in the structure and, thus, function of plasma and endocellular membranes. In adults, it is the main component of myelin and nerve cells, making it indispensable for the maintenance of neuronal plasticity and conductivity. Yet, the interactions leading to the pathologies considered here involve essentially membrane and transmembrane proteins in interaction with neighboring lipids;

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