

Organic-Bio-Chemistry (From Soap to Amyloid Proteins)

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This branch of science is concerned with the study of structures, chemical composition, properties and chemical reactivity of organic compounds and materials. Organic compounds and organic chemicals in biology form the bases of life on our planet and are mainly hydrocarbons but can contain also other elements as oxygen, nitrogen, sulfur, phosphorus, organometallic compounds as sodium, potassium... etc., alkaline earth metals as magnesium, transition metals as Zinc, Copper, Cobalt... etc. or other metals as aluminum. The vital force theory developed before the 19th century differentiated organic compounds obtained from living organisms from the inorganic compounds. Since organic compounds existed often as mixtures, then varieties of techniques were developed for separation, characterization and purity assessment through the following: distillation, crystallization, solvent extraction, mass spectrometry-NMR, centrifugation, electrophoresis and chromatography i.e. HPLC and gas chromatography.

The first organic compound recorded was SOAP in 1816 by Michel CHEVREUL by adding alkali to fats, followed in 1828 by Friedrich WOHLER who produced UREA using the inorganic ammonium cyanate salt and in 1856 W.H. PERKIN manufactured accidentally an organic dye called PERKIN'S MAUVE instead of quinine. By the second half of the 19th century were developed synthetic indigo replacing those produced earlier from plants and at the same time pharmaceutical industry began manufacturing acetylsalicylic acid (aspirin). Early 20th century Polymers, Enzymes were shown to be large organic molecules and Petroleum was shown to be of biological origin and later on Petro-chemistry introduced various synthetic chemicals. The study of proteins and nucleic acids became more and more accelerated through Biochemistry leading to a better understanding of diseases specially those caused by misfolded protein aggregates i.e. amyloid proteins.

Protein misfolding diseases (Amyloidosis)

Amyloid proteins are insoluble, aggregated and inappropriately folded versions of proteins or polypeptides present naturally in the body and their deposition within cells render the protein dysfunctional. The change from normal forms to amyloid one is associated with conformational changes in the peptide back-bond from a higher degree alpha-helical structure to a conformer in which a much higher degree of beta-sheet structure are present. More than 20 serious human diseases are reported as Alzheimer's disease (A β), Parkinson's disease (Alpha-synuclein), Diabetes mellitus type 2 (Amylin), Medullary carcinoma of the thyroid (ACal), Cardiac arrhythmias (AANF), Rheumatoid arthritis (AA), Lattice corneal dystrophy (AKer), Cerebral amyloid angiopathy (ACys), Dialysis related amyloidosis (Beta 2 microglobulin)...etc. The severity and prediction of the disease depends on the fate of the misfolded protein which may become non-functional, sub optimally functional or it may be degraded after tagging with heat shock proteins by the cellular machinery.

Amyloids are characterized by a cross-beta sheet quaternary structure and usually were identified by using indirect measurements with fluorescent dyes, stain polarimetry, circular dichroism, or FTIR. Better identification of the cross-beta fibres (observation of one longitudinal and one transverse diffraction lines) is by placing the sample in an X-ray diffraction beam.

Some of these misfolded amyloids are infectious proteins named Prion (PrP^{sc}) are the causative agent of the neurodegenerative diseases in animals and man [1]. Upon infection with prions conformational changes in the normal cellular glycoprotein (PrP^c) leading to propagation of a beta-sheet conformed, detergent insoluble and proteinase K (PK) resistant pathogenic protein. The accumulation of the PrP^{sc} is associated with a wide range of Transmissible Spongiform Encephalopathy's (TSE), including scrapie in sheep and goats, spongiform encephalopathy in cattle (BSE), chronic wasting disease in deer and Creutzfeldt-Jakob disease in humans (CJD).

Streptomycin and Proteins

Streptomycin was shown in the year 1940 to interact with globulin and albumin during dialysis studies. By accident we also observed the interaction of streptomycin with the prion proteins and later with the Alzheimer peptide P53 and demonstrated the ability of streptomycin to form multimolecular aggregates with the pathogenic prion protein and their recovery via a low-speed centrifugation step. The addition of increasing quantities of streptomycin to constant amount of brain extracted and PK treated (PrP^{sc}), followed by electrophoresis on 15% polyacrylamide gel, transfer and immunodetection revealed an increase in the molecular mass of each of the 3 PrP^{sc} bands proportional to the quantity of streptomycin added. The interaction of streptomycin with proteins is optimum at alkaline PH and take place through hydrogen bond transfer between the two guanidine groups present on streptomycin and the amino-acids of one or several prion proteins. Many chemical molecules sharing common chemical function with streptomycin (harboring 2 guanidine groups) as dihydrostreptomycin, bis-3-aminoproylamine, guanidine hydrochloride and spermine tetrahydrochloride reproduced aggregation and precipitation of the PrP^{sc} ruled out the possibility of a Schiff-base reaction [2].

Immunochemical detection techniques as western-blot, Elisa... etc. using streptomycin were developed for better prion detection in disease samples [2]. The interaction of streptomycin with proteins leads to an amplification of their immunological detection either due to the presence of protein aggregates but as well to the presence of hydrogen bonds on the protein surface allowing better attachment of the monoclonal antibodies to their epitopes. The introduction of streptomycin sulfate also in immune-histochemical detection resulted in earlier diagnosis and accurate cellular and regional mapping of the PrP^{sc} deposition in several animal TSEs [3].

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Received September 15, 2014; Accepted September 15, 2014; Published September 25, 2014

Citation: Moussa A (2014) Organic-Bio-Chemistry (From Soap to Amyloid Proteins). J Chromatograph Separat Techniq 5: e125. doi:10.4172/2157-7064.1000e125

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The issue of the interaction of streptomycin with PrP^{sc} after inoculation of mixtures intraperitoneally into mice revealed reduced to even absence of accumulated prion infectivity marker in the spleen 45 days post inoculation. This drop in infectivity can be attributed to changes of the surface electric charges due to hydrogen bond transfer between the two guanidine groups present on streptomycin and the different amino acids on the PrP^{sc} peptides [4]. Also it was reported that guanidine hydrochloride possess antibacterial activity and can inactivate the pathogenic prion protein providing evidence that the 2 guanidine groups are essential for the biological activity of streptomycin and related chemicals and also for their antibacterial activity.

Future researches should be directed towards incorporation of streptomycin in protein detection techniques especially in cancer diagnosis. Also streptomycin can be used for inactivation of enzymes

or infectivity reduction of different proteins or even viruses. Finally protein aggregation activity of streptomycin can be of benefit in soil biology.

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