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Review

Adaptive Membrane Fluidity Modulation: A Feedback Regulated Homeostatic System Hiding in Plain Sight

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Abstract. *The structure of the plasma membrane affects its function. Changes in membrane fluidity with concomitant effects on membrane protein activities and cellular communication often accompany the transition from a healthy to a diseased state. Although deliberate modulation of membrane fluidity with drugs has not been exploited to date, the latest data suggest the "druggability" of the membrane. Azelaic acid esters (azelates) modulate plasma membrane fluidity and exhibit a broad range of immunomodulatory effects in vitro and in vivo. Azelates represent a new class of drugs, membrane active immunomodulators (MAIMs), which use the entire plasma membrane as the target, altering the dynamics of an innate feedback regulated homeostatic system, adaptive membrane fluidity modulation (AMFM). A review of the literature data spanning >200 years supports the notion that molecules in the MAIMs category including known drugs do exert immunomodulatory effects that have been either neglected or dismissed as off-target effects.*

A literature search was conducted using PUBMED, MEDLINE, and Library of Congress databases to capture peer-reviewed research articles (including reviews and meta-analyses), published through August 27, 2021, with the earliest record dating from 1801. The search terms included "plasma membrane" AND "fluidity" OR "plasticity" OR "rigidity". Secondary searches combined keywords consisting of individual chemical entities listed in this manuscript (for example, cholesterol, ethanol, turpentine) and physiological conditions (for example pain, fever, disease). The collected abstracts and/or full papers were surveyed by both authors in order to confirm article relevancy to the topic.

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Plasma Membrane at the Crossroads of Communication in Health and Disease

The plasma membrane of eukaryotic cells plays an active role in the flow of information between cells and their environment (1, 2). Variations in the composition of membrane lipids affect the membrane fluidity and membrane environment has an impact on integral and membrane-associated proteins with consequences for the entire organism (3-6). In transition from a healthy to a diseased state, cellular plasma membranes usually become more rigid (5, 7, 8) mainly due to incorporation of cholesterol (9) that is dynamically exchanged between the blood and plasma membranes (9, 10). High blood cholesterol correlates with various diseases (11-14) while positive health effects can be achieved upon lowering cholesterol content of the plasma membrane (15-17).

Structural changes in cellular plasma membranes have been mainly focused on the role of membrane structural integrity "in sickness and health" (18, 19), although membrane domains were also proposed as possible drug targets (20). Intentional pharmacological tuning of membrane fluidity with drugs has received little attention but on closer examination there is a significant amount of data suggesting the "druggability" of the fluidity of cell membranes. The hypothesis that one can affect the activities

of membrane-associated proteins through alterations in plasma membrane fluidity using lipid-soluble molecules with application in the treatment of human and animal diseases is supported by our experimental data on the effects of esters of azelaic acid (azelates) that act as membrane fluidizers and exert immunomodulatory effects *in vitro* and *in vivo* (1, 21-23). Unlike targeted therapies that usually focus on single molecular entities, the target for azelates is the entire plasma membrane. Azelates have been recognized as the first representatives of a novel class of drugs, membrane active immunomodulators (MAIMs) (1).

MAIMs and Adaptive Membrane Fluidity Modulation (AMFM)

This concept built upon experimental data has been described elsewhere (1) and is briefly summarized below. We postulated that MAIMs change plasma membrane fluidity and that membrane fluidity is homeostatically controlled *via* an innate feedback mechanism, Adaptive Membrane Fluidity Modulation (AMFM), an active process of plasma membrane fluidity regulation in mammalian cells. Our AMFM hypothesis expands and extends the historical concept of homeoviscous adaptation (24) and proposes a mechanism directed to the regulation of biochemical processes driven by the physiological modulation of plasma membrane fluidity.

The temperature of the human body, and those of all warm-blooded animals outside of hibernation, is regulated in a narrow temperature range. For humans the normal body temperature is around 36.6˚C. Body temperature varies in pathologic states between 35˚C (hypothermia) and high fever at around 42˚C. We propose that body temperature control is essential to maintaining cellular plasma membrane fluidity and thus membrane protein function. What, one must ask, is the "purpose" of fever. That is to say, what survival advantage does the ability to mount a fever confer? Most pathogens are unaffected by the modest temperatures attained in human fever despite superstitious beliefs that fever was somehow involved in killing them. We propose that fever may be directed to regulating inflammatory mediator trafficking. Everyone who has had a fever has also had the experience of the fever" breaking" with subsequent resolution of the hyperthermic state and improvement in subjective feelings of wellbeing. The AMFM hypothesis sheds a new light on these innate processes, on targeted therapies and receptor-directed mechanisms of action of hormones, drugs and toxins (1).

MAIMs Hiding in Plain Sight

A review of the biomedical literature related to the modulation of plasma membrane published over the past two hundred years has led us to the conclusion that many known drugs, natural products, and synthetic molecules have membrane fluidity modulating properties and can be viewed, at least in part, as MAIMs. The biochemical effects of these MAIMs have been well documented in the medical literature but the underlying AMFM system on which they exert their effects has remained largely unappreciated. We have grouped these molecules into three broad categories: drugs, natural products, and synthetic molecules. We further discuss representative molecules in each category in the light of their membrane modulatory activities.

There are numerous examples of drugs, many of them derived from natural sources, that are also MAIMs. For example, the fatty acid azelaic acid has been used in the treatment of dermatological diseases for decades (25, 26). Diethyl azelate, a natural product made by plants and animals and unwittingly used by humanity over many millennia (27-34), is also a promising drug candidate (21).

Tecfidera (dimethyl fumarate) was first used in the treatment of psoriasis and has been repurposed for the treatment of multiple sclerosis (35) but its mechanism of action of remains unclear. Dimethyl fumarate is known to have immunomodulatory properties (36) and most of the affected targets have antioxidant and/or anti-inflammatory functions (37). Tecfidera is used in the clinic at doses of hundreds of milligrams per day. In addition, the drug is an allergic sensitizer at low picomolar levels (38).

Ethanol is natural product and also a drug. Human consumption of ethanol rendered from wheat in the form of beer dates back at least 10,000 years (39). The date that humans recognized the pharmacological effects of ethanol intake is lost to history. The medical community has reported on its effects starting as early as 1805 and continuing through the present day (40-42). Ethanol has no known receptor, is a membrane fluidizer at low doses (43) and displays a non-monotonic effect on lipid chain order in a striking contrast to methanol (44, 45). Ethanol is known to modulate the activity of GABA A receptors, glycine receptors and two pore potassium channels (46).

The organosulfur compound dimethyl sulfoxide (DMSO) enhances the cell membrane penetration of drugs or DNA and enhances percutaneous absorption when used in combination with other substances. *In vitro* data supported by molecular dynamics simulations suggest that increasing concentrations of DMSO induce membrane undulation and thinning, followed by pore formation and eventually bilayer collapse (47). DMSO can also provide a rapid albeit temporary relief of arthritic pain (48) and has some utility in wound healing (49).

General anesthetics such as isoflurane, propofol, phencyclidine, and noble gases (Xe, He) also lack known receptors and behave in a manner similar to ethanol (37, 44, 50-52). Ether, the oldest general anesthetic, was first reported in 1851 to induce glucosuria (53). It was thought at the time

that the nervous system or emotional factors were responsible for these observations (54). Plasma membrane involvement was highlighted by a report on the effect of isoflurane on vesicle exocytosis and calcium channels (55). Direct demonstration of targeting of plasma membrane lipids by inhalational of anesthetics led to the proposal of a mechanism that involves disruption of lipid rafts (56).

Antibiotics, such as tetracyclines, cross the plasma membrane and their activity is related to transmembrane flux (57). Tetracyclines are also known to act by interfering with protein synthesis at the ribosome by inhibiting attachment of the aminoacyl-tRNA to the A site. Thus, tetracycline mode of action encompasses a defined protein target and a membrane modulatory mechanism. The anticonvulsant, phenytoin, causes voltage-dependent block of voltage gated sodium channels (58). Hexamethylene bisacetamide, a differentiating agent, is an amphipathic molecule that perturbs membrane-protein interactions and segregates lipids in discrete domains (59).

Decamethonium bromide, a muscle relaxant, is a membrane depolarizer (60) that interacts with plasma membrane components through hydrophobic interactions, Van der Waals forces, and ion pairing. Phospholipid drugs exemplified by miltefosine, edelfisone, and perifosine displace proton pump protein from lipid rafts and alter cholesterol trafficking (61-63).

The activities of many drugs can be accounted for more fully by inclusion of both target/receptor mediated activity and MAIM activity. For example, the histone deacetylase inhibitors suberoylanilide hydroxamic acid and valproic acid affect expression of plasma membrane receptors and also display membrane disordering activity (45, 64).

Aspirin, a pharmacological Swiss army knife, exerts a wide range of effects ranging from analgesic, antipyretic and anti-inflammatory activities, cardiovascular benefits, to cancer prevention (65). According to the commonly accepted mechanism of action, aspirin inhibits cyclooxygenase (66). A small human study using high doses of aspirin reportedly improved glucose tolerance and lowered insulin resistance and the clinical activity of aspirin was explained in terms of specific inhibition of the serine/threonine kinase cascade (67). Yet proposed mechanisms of action do not convincingly explain the breadth of known effects of aspirin. Since aspirin increases plasma membrane fluidity and prevents formation of lipid rafts through non-specific interactions with lipid membranes (68), we propose that aspirin functions as a MAIM and thus shares similar features with diethyl azelate (DEA). An immunomodulatory activity of aspirin was postulated in the past (69) but the concept has not gained much attention.

The second category of MAIMs encompasses natural products, many of which are used as drugs. Our observations of the immunomodulatory activities of azelates are echoed in the biological activities of some natural products. Polyunsaturated fatty acids such as omega-3 and omega-6 fatty acids affect membrane fluidity when incorporated into phospholipids (70). Direct binding of omega-3 fatty acids to the cellular receptor FFA4 changes calcium influx across the plasma membrane (71). Trans fatty acids incorporate into lipid rafts and can induce tumor growth in some cases (72). Medical uses of turpentine oil composed of terpenes obtained by the distillation of pine resin were reported in the early 19th century (73, 74). Terpenes are also known to transiently affect cellular signaling (75).

Carotenoid pigments increase plasma membrane rigidity in *Staphylococcus aureus* (76). Exogenous carotenoids have beneficial effects in human disease prevention (77). Most polar carotenoids span the lipid bilayer, rigidify the membranes and limit oxygen penetration to the hydrophobic membrane core susceptible to oxidative degradation (78). Natural polyphenols produced in plants as secondary metabolites, are a large part of the human diet (79) and have pharmacological properties that include anti-coronavirus and immunomodulatory activities (80). The most abundant polyphenols such as flavonoids inhibit plasma membrane ATPase and maintain ion cellular homeostasis (81). A review of plant-derived immunomodulators with immunosuppressive properties was focused on their potential to calm the cytokine storm (82), presumably due to membrane interactions. For example, luteolin intercalates within cell membranes leading to their disruption (83). Resveratrol, a natural phenol, apparently targets the entire cell membrane and affects the intramembrane ion transport (84). Curcumin, another well-known polyphenol, has membrane-thinning properties (85), decreases membrane rigidity but drastically stiffens the bilayers in model membranes with high cholesterol content (86). Curcumin modulates the function and expression of structurally and functionally unrelated membrane proteins (87).

The third category of MAIMs is represented by amphiphilic synthetic molecules that often contain halogens. Organic halogen compounds are a large class of chemicals that contain one or more halogens (fluorine, chlorine, bromine, or iodine) combined with carbon and other elements. Notorious polyfluorinated compounds such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are persistent in the environment and have been shown to cause membrane disruption and oxidative damage in model systems (88). Some halogenated organics are endocrine disruptors that can interfere with endocrine systems (89). Most toxicants, including endocrine disruptors, have a U-shaped dose response curve. This type of dose response, known as hormesis (90), defies the toxicological dogma of "the dose makes the poison". For example, endocrine disruptors can have effects at low doses that are not predicted by effects at higher doses (91). There are important toxicological implications of the AMFM hypothesis. The endocrine disruptors are biologically persistent due to their poor metabolism and slow elimination. They are associated with diseases characterized by

derangement of innate and adaptive immunity in those primarily exposed and their offspring (92). The environmental impact of these "bad MAIMs", or shall we say, "forever MAIMs," is underappreciated. As the list is very long, we will highlight just a few notorious examples.

The fungicide vinclozolin binds to membrane androgen receptor (93). Organophosphate pesticides have been shown to decrease erythrocyte membrane fluidity (94). Dioxins (*e.g.*, Agent Orange) contain 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) that alters plasma membrane function (95). In fact, dioxin insult may induce azelate levels (28), an effect that can be viewed as a chemoprotective response of endogenously produced azelate. The industrial surfactant perfluorooctanoic acid is present in many household products including stain-resistant carpets, microwave popcorn bags, and dental floss. Perfluorooctanoic acid causes irreversible plasma membrane injury in acute exposure (96), is present in the blood of 98% of the US population, and is linked to increased cancer rates (97). Commonly used bisphenol plasticizers alter calcium cellular entry in a non-monotonic manner (98). Bisphenol A acts as a selective estrogen receptor modulator and initiates rapid responses *via* estrogen receptors presumably associated with the plasma membrane (99). Most humans are exposed to phthalate plasticizers with adverse effects on human reproduction (100). Dimethyl phthalate has been shown to directly damage bacterial cell walls (101).

Physiological Support for the AMFM Hypothesis

The AMFM hypothesis is supported by a wealth of observations of physiological processes. Fever is probably the most obvious case. The role of fever was queried in 1805 (102) and a report on the effect of acute fever on glycosuria appeared in 1885 (103). The peri-ovulation body temperature spike is well known (104) but its mechanism, and purpose, is not well understood though the fact that fertilization involves the fusion of the sperm with the egg suggests the possibility that the temperature spike may facilitate the process. It is not surprising that elevated temperature increases membrane fluidity thus when body temperature increases during a high fever, the fluidity of cell plasma membranes also increases. As a result, proteins and other membrane components become more mobile within and through the membrane.

The role of fever in higher organisms is thought to disfavor pathogen survival in hosts as diverse as locusts, snails, finches, iguanas, rabbits and humans (105, 106). Colloquially, many laymen and even numerous scientists and physicians labor under the tragically flawed idea that the purpose of fever is to kill pathogens. However, a growing body of evidence supports the idea that fever confers a survival advantage in the form of disease tolerance to host animals.

Additional illustration of the AMFM action include fluctuations of blood glucose, insulin, and lipids under normal physiological conditions or in the response to infections or drugs. Examples include increased triglyceride levels and insulin resistance in pregnancy (107, 108), high triglyceride levels associated with multiple diseases (109), and diabetogenic effects of statin therapy (110). The association of obesity with dyslipidemia and insulin resistance is well documented (111, 112) but a less known consequence of obesity may be hampering immune responses to SARS-CoV-2 vaccine (113).

A recent report on cholesterol metabolites that facilitate innate immunity to bacterial infections by mobilizing cell surface accessible cholesterol sheds a new light on the feedback loop involving a signal-mediated membrane remodeling pathway (114). The implications of this finding go far beyond the cellular response to bacterial pathogens. Cholesterol has also been shown to affect the function of some G protein–coupled receptors (GPCRs) (115), the largest family of integral membrane proteins involved in cellular signal transduction. A molecular sensor for cholesterol in a human GPCR has recently been identified (116) supporting the notion of a direct relationship between membrane lipids, proteins, and cellular signaling.

Since anesthesia directly affects plasma membrane fluidity, it is quite interesting that anesthesia by itself or in association with surgical procedures can lead to rapid adaptive changes in blood glucose, insulin, and lipids. In rodents, plasma glucose and insulin increase in response to anesthesia in the absence of surgical stress (117). In human studies, hyperinsulinemic and normoglycemic clamp after heart surgery caused elevation of blood lipids (118). Short-term propofol anesthesia significantly raised triglyceride levels in pediatric patients (119). Elevated risk for perioperative hyperglycemia observed in non-diabetic subjects but not in diabetic patients (120) was referred to as paradoxical. For us the effect is akin to improved control of glucose by DEA in subjects with higher levels of hemoglobin A1c (21).

"Forever MAIMs" also affect lipid and glucose levels. Exposure to perfluoroalkyl substances PFOAs increases the risk for insulin resistance and type 2 diabetes, and disrupts lipid and weight regulation (121, 122). Dioxins such as TCCD alter lipid metabolism in rodents (123). Human epidemiologic studies suggested elevated risk of type 2 diabetes and an increase of its hallmark, insulin resistance (124).

Other supportive evidence comes from documented effects of diet on human health. Increased incidence of diabetes, heart disease and cancer are associated with excessive ethanol intake, while health benefits of Asian diet with fermented soy, Mediterranean diet with wine and olive oil, and other dietary fats such as fish and vegetable oils are widely acknowledged. Observations on the efficacy of olive oil for preventing and curing the plague were reported in 1801 (125).

It Is About Time. The First Minutes of MAIMs Action

As presented above, physiological effects of MAIMs on cellular signaling through the adaptive feedback response in the form of transcriptional, translational and post-translational events happen on the time scale of hours to days. In contrast, local membrane effects of MAIMs translate to acute systemic responses that can be observed within minutes.

Inhalational anesthetics exert their effects in less than 5 min (126). For orally administered MAIMs, either drugs or foods, the timing can be equally short. Low nanomolar doses of nitroglycerin cause immediate decrease in the mean diastolic blood pressure in rats, and a single sublingual dose of nitroglycerin affects hemodynamic parameters in humans in 2-5 min (127). The effects are consistent with rapid absorption of nitrates from mucous membranes, the gastrointestinal tract, and the skin (128). Regional effects of ethanol intoxication manifested as cerebral blood flow effects are observed in 5 min (129). DMSO applied topically quickly causes a distinctive garlic taste on the tongue that is indicative of a speedy transport through skin and mucosa (130). Resveratrol which apparently uses the entire membrane as the target (84), used in a lozenge formulation for oral transmucosal delivery reached maximum plasma concentration in 15 min (131). Significant changes in flow-mediated dilation are seen in 30 minutes of grape polyphenol supplementation (132). Given that it takes blood 20 seconds to circulate through the whole body (133), a single dose of an oral MAIM can rapidly achieve systemic effects.

Concluding Remarks

The AMFM hypothesis does not account for the receptor or molecular target mediated activities of these compounds but it provides insight to the source of those activities that are not accounted for by receptor or specific target effects. Our understanding of the AMFM system opens the door to developing novel treatments for diseases including diabetes, cardiovascular, infectious and autoimmune diseases, stroke, cancer, biodefense indications and many others. AMFM is likely to be a valuable addition and/or complement to the current targeted therapies and receptor-directed mechanisms of action of hormones, drugs and toxins.

Conflicts of Interest

EI and RTS are the owners and officers of New Frontier Labs, LLC.

Authors' Contributions

EI and RTS formulated the theoretical concepts based on own research data, performed literature searches, and wrote the manuscript.

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