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Phospholipid, arachidonate and eicosanoid signaling in schizophrenia

Erik Messamore[1] and Jeffrey K. Yao[2,3,4,⋆]

[1] University of Cincinnati and Lindner Center for Hope, Cincinnati, OH, USA
[2] VA Pittsburgh Healthcare System, Pittsburgh, PA 15240, USA
[3] Department of Psychiatry, Western Psychiatric Institute Clinic, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA
[4] Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA 15213, USA

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Abstract – This paper reviews the potential role of arachidonic acid in the pathophysiology of schizophrenia. We discuss how abnormal levels of arachidonic acid may arise, and how dysregulation of signaling molecules derived from it have the potential to disrupt not only dopamine signaling, but numerous other physiological processes associated with the illness. Pharmacological doses of niacin stimulate the release of arachidonic acid; and arachidonic acid-derived molecules in turn dilate blood vessels in the skin. A blunted skin flush response to niacin is reliably observed among patients with schizophrenia. The niacin response abnormality may thus serve as a biomarker to identify a physiological subtype of schizophrenia associated with defective arachidonic acid-derived signaling.

Keywords: Phospholipids / arachidonic acid / eicosanoids / niacin-induced flushing, endophenotype marker / schizophrenia

Résumé – Signalisation des phospholipides, de l'arachidonate et de l'écosanoïde dans la schizophrénie. Cet article examine le rôle potentiel de l'acide arachidonique dans la physiopathologie de la schizophrénie. Il est discuté comment des niveaux anormaux d'acide arachidonique peuvent survenir, et comment la dérégulation des molécules de signalisation qui en découle est capable de perturber non seulement la signalisation de la dopamine, mais aussi de nombreux autres processus physiologiques associés avec cette maladie. Des doses pharmacologiques de niacine stimulent la libération d'acide arachidonique ; des molécules dérivées de l'acide arachidonique dilatent à leur tour les vaisseaux sanguins dans la peau. Une brusque rougeur de la peau en réponse à la niacine est observée de manière constante parmi les patients atteints de schizophrénie. La réponse anormale à la niacine peut donc servir de biomarqueur afin d'identifier un sous-type physiologique de la schizophrénie, associé à un système défectueux de signalisation des dérivés de l'acide arachidonique.

1 Introduction

Schizophrenia (SZ) is a complex behavioral syndrome associated with diverse biochemical and physiological abnormalities. This paper will describe how arachidonic acid (AA) and abnormalities related to its metabolism may to some extent unify some seemingly unrelated biochemical findings in SZ (Horobin, 1998; Skosnik and Yao, 2003). We will also describe how a blunted skin flush response to niacin may serve as a biomarker for AA-related signaling defects, and suggest that AA-related abnormalities may represent a distinct physiological subtype within the SZ syndrome (Messamore, 2003; Messamore *et al.*, 2010; Yao *et al.*, 2015).

⋆ Correspondence: jkyao@pitt.edu

2 Heterogeneity of the Schizophrenias

Despite early acknowledgement of the likelihood that SZ is not a unitary illness (Bleuler, 1920), for most of the 20th century it was usually studied as if it were a single disease entity. The dominant view was that of a unitary illness with differing modes of expression. This view of SZ, however, is no longer tenable. The variable therapeutic response to antipsychotic medication provides strong evidence against a unitary cause of SZ (Garver *et al.*, 2000). In fact, the preponderance of evidence is consistent with SZ having numerous, etiologically distinct causes (Jablensky, 2006). Efforts toward understanding its various causes, and toward developing improved, etiologically-focused treatments, may be more fruitful if the schizophrenias were deconstructed into physiologically-based

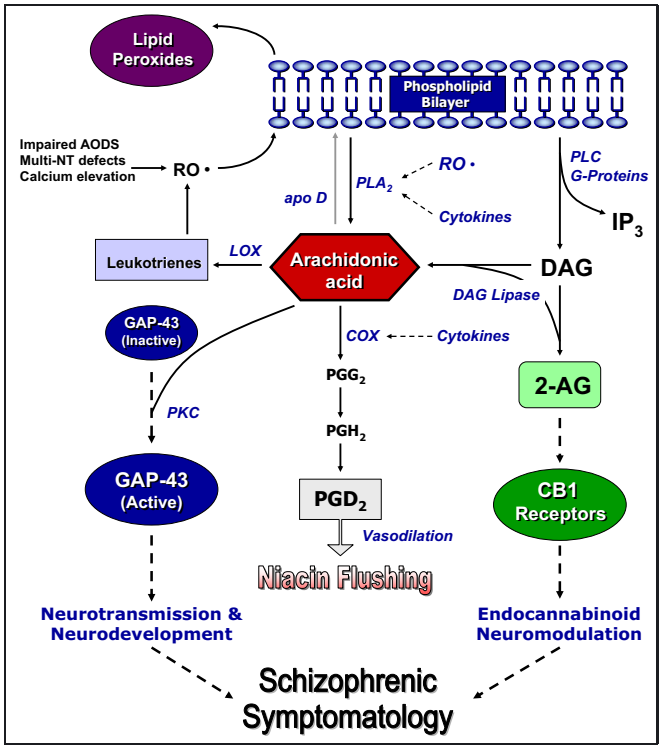

Fig. 1. An overview of phospholipids turnover, arachidonic acid, and eicosanoid signaling in schizophrenia symptomatology (adapted from Skosnik and Yao, 2003). Abbreviations: AODS, antioxidant defense system; NT, neurotransmitters; RO, reactive oxygen species; apoD, apolipoprotein D; PLA_2, phospholipase A_2; PLC, phospholipase C; LOX, lipooxygenase; AA, arachidonic acid; DAG, diacylglycerol; COX, cyclooxygenase; 2-AG, 2-arachidonoyl glycerol; GAP, growth-associated protein; PKC, phosphokinase C; PGG_2. prostaglandin G_2; PGH_2, prostaglandin H_2; PGD_2, prostaglandin D_2; CB, cannabinoid.

intermediate phenotypes (Braff *et al.*, 2007; Keshavan *et al.*, 2008). We and others have observed evidence suggesting that one of these intermediate phenotypes may involve phospholipid signaling abnormalities that prominently involve dysregulation of AA levels or the actions of its physiologically active metabolites.

3 Phospholipid, arachidonate and eicosanoid (PAE) signaling in SZ

A phospholipid turnover abnormality is present in many cases of SZ. Disordered phospholipid turnover with resulting changes in the levels and metabolic destinations of AA can unite seemingly unrelated neurochemical and clinical observations in SZ.

A model relating phospholipid signaling to SZ-relevant neurochemical abnormalities can be found in Figure 1. As shown, several factors – including oxidative stress and cytokine release – have the potential to lyse membrane phospholipids, resulting in the release of AA and, over time, reduce its cell membrane levels. Overactivity of phospholipase A_2 (PLA_2) or phospholipase C (PLC) enzymes would deplete the membrane-lysable pool of AA. In turn, changes in the availability of AA and AA-derived signaling molecules affect the release or circulating levels of several neuroactive molecules, including: GAP-43; the neurotransmitters dopamine and glutamate, and the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG). Alterations in AA may also affect the inflammatory response, which can then affect PLA_2 release *via* cytokines, further exacerbating phospholipid turnover and AA release. These diverse disruptions have the potential to impact many neuronal signaling pathways relevant to psychosis (Horrobin, 1998; Peet *et al.*, 1994; Skosnik & Yao, 2003).

Low levels of AA have been observed postmortem in the cerebral cortex of SZ patients (Horrobin *et al.*, 1991; Yao *et al.*, 2000). Low AA levels have been identified in red blood cell (RBC) membranes from patients with chronic SZ (Glen *et al.*, 1994; Peet *et al.*, 1994; Vaddadi *et al.*, 1986; Yao *et al.*, 1994a), as well as first-episode neuroleptic-naïve SZ (Avrindakshan *et al.*, 2003; Reddy *et al.*, 2004). Thus, abnormally low AA levels have been observed in brain as well as RBC membrane phospholipids from patients with SZ (further reviewed by Conklin *et al.*, 2007; Peet, 2007; Skosnik and Yao, 2003; Yao, 2003). These changes could conceivably lead to decreased synthesis of eicosanoids. Collectively, these changes can account for numerous physiological and clinical observations in SZ.

Utilizing varying types of samples (*e.g.* plasma, RBC, platelets, postmortem brain, etc.) and methodologies (^{31}P Magnetic resonance spectroscopy, platelet function, niacin-induced flushing, etc.), somewhat consistent patterns of decreased polyunsaturated fatty acids (PUFAs) and increased phospholipid turnover are apparent (Bentsen *et al.*, 2011; Horrobin, 1998; Mahadik and Yao, 2006, Peet, 2007; Pettegrew *et al.*, 1991; Skosnik and Yao, 2003; Yao *et al.*, 1994a), particularly in relation to AA.

In addition to the formation of second messengers, AA released from membrane phospholipids can be converted to a variety of biologically active metabolites, collectively termed eicosanoids, through the concerted reactions of cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P-450 (CYP). Eicosanoids can modulate neural cell function, and can mediate several pathophysiological processes (Bazan, 2006). Since AA is the major C20 polyunsaturated fatty acid (PUFA) in mammalian tissues, the prostaglandin-2 (PG2) and thromboxanes-2 (TX2) series are the predominant classes of eicosanoids (Fig. 2). Inhibition of COX by nonsteroidal anti-inflammatory drugs has revealed the significance of PG2 in the regulation of nerve conduction, neurotransmitter release, inflammation, pain, fever, immune responses, apoptosis and psychosis (Akhondzadeh *et al.*, 2007).

4 Clinical and physiological effects of AA and eicosanoids

AA deficiency, or abnormal regulation of AA-derived signaling could explain several clinical and physiological findings in SZ. Association between low RBC membrane AA levels and the expression of the negative symptom syndrome (apathy, social withdrawal, affective flattening, etc.) has been reported (Glen *et al.*, 1994). In other studies, low RBC

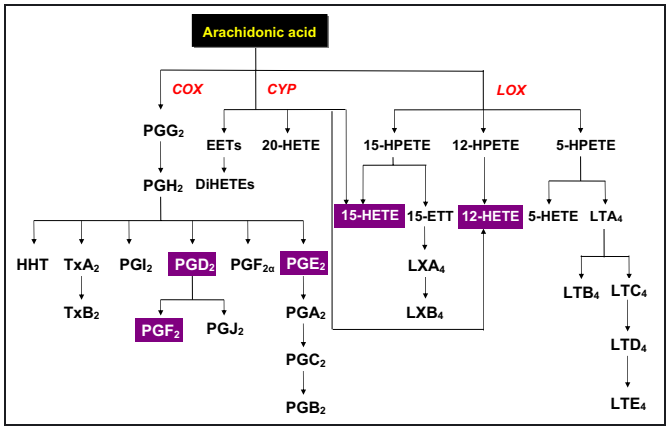

Fig. 2. Arachidonic acid cascade (adapted from Condray and Yao, 2011). EET, PGI_2, PGD_2, PGE_2, PGF_2, 12-HETE and 15-HETE are considered as potential vasodilators.

membrane levels of dihomo-γ-linolenic acid, the immediate precursor of AA, were associated with increased psychosis ratings (Yao *et al.*, 1994b) and disorganized symptoms (Doris *et al.*, 1998). Among SZ patients receiving fatty acid supplementation therapy, increased RBC AA contents were associated with a reduction in the severity of symptoms (Peet *et al.*, 2002).

Aspirin inhibits vascular dilation during electrical stimulation of cerebral cortex slices *in vitro* (Zonta *et al.*, 2003); and pharmacological inhibition of COX-2, or COX-2 gene knockout, reduces by 40 to 50% the cerebral blood flow response of the sensory cortex to whisker stimulation in mice (Niwa *et al.*, 2000). Thus, an eicosanoid signaling abnormality could potentially contribute to the cerebral neurovascular coupling defects that have been repeatedly observed in SZ (Berman *et al.*, 1992; Liddle *et al.*, 1992; Weinberger *et al.*, 1992).

Many signs and symptoms of SZ are suggestive of excess dopamine activity (Snyder, 1981). Prostaglandin D_2 (PGD_2) and other PGs stimulate the production of cAMP and thereby exert functional antagonism of dopamine-D_2 receptors, which modulate inhibition of cAMP synthesis (Ono *et al.*, 1992; Wanibuchi and Usuda, 1990). PGD_2 therefore counteracts the biochemical and behavioral effects of dopamine *in vitro* and *in vivo*. PGD_2 administration blocks the behavioral effects of dopaminergic agents such as apomorphine, L-DOPA, and amphetamine; and induces catalepsy in a manner identical to dopamine-D_2 receptor antagonists such as haloperidol (Ono *et al.*, 1992; Wanibuchi and Usuda, 1990). Deficient PGD_2 signaling would thus be expected to produce the signs of excessive dopamine activity that are seen in SZ. A role for PGs as endogenous anti-dopaminergic agents is supported by the findings that inhibitors of PG synthesis can cause psychotic symptoms in some people and can worsen psychotic symptoms in SZ patients (Hoppman *et al.*, 1991; Sussman and Magid, 2000). The relationship between SZ and COX products is complex, however, as there are also reports suggesting that COX inhibitors may augment the efficacy of antipsychotic medications (Akhondzadeh *et al.*, 2007; Laan *et al.*, 2010; Müller *et al.*, 2002). These seemingly contradictory findings nonetheless speak to the relevance of prostaglandins to the pathophysiology of the schizophrenias while also pointing toward their etiologic diversity.

A deficiency of prostaglandins has previously been related to SZ (Horrobin, 1977). It is likely that reduced AA availability may in part explain a variety of clinical observations that are usually ignored by the receptor-based etiological hypotheses (Horrobin, 1998). For example, in SZ, there appears to be a lower risk of arthritis and other inflammatory diseases (Eaton *et al.*, 1992), greater resistance to pain (Davis *et al.*, 1979, Horrobin, 1977), and remission of psychosis during fever has been observed (Horrobin, 1977). These effects could be secondary to reduced eicosanoid signaling.

5 Niacin Flush response as a test for eicosanoid abnormalities

Niacin (nicotinic acid), at sufficient doses, is well-known to dilate blood vessels in the skin resulting in a visible skin flush. The biochemical mechanism (Fig. 3) of this response has been studied over the course of several decades so many of the key steps have been well described. Niacin-induced skin flushing is prominently mediated by metabolites of AA. Thus, it may serve as a physiological marker of the integrity of phospholipid-arachidonate-eicosanoid (PAE) signaling. We will now describe how the niacin response abnormality might define a physiologically distinct subtype of SZ.

6 Mediation of niacin flush by AA metabolites

The levels of PGD_2 and 9α,11β-PGF_2 (a stable metabolite of PGD_2) rise markedly in skin exudate or venous blood following oral or topical administration of niacin in humans (Eklund *et al.*, 1979; Kobza Black *et al.*, 1982; Morrow *et al.*, 1992). Evidence favors PGD_2 as the predominant mediator of the flush response (Morrow *et al.*, 1989). However PGE_2 levels also increase in response to niacin (Eklund *et al.*, 1979; Kobza Black *et al.*, 1982). In man, the flush response to niacin can be completely abolished by COX inhibitors such as aspirin or indomethacin (Svedmyr *et al.*, 1977; Wilkin *et al.*, 1982). In mice, the flush response to niacin can be eliminated by knocking out genes for either the niacin receptor or COX-1, consistent with an exclusive and obligatory role for this pathway in niacin-evoked skin flushing (Benyó *et al.* 2005). Classical vasodilatory mediators, such as histamine, bradykinin, serotonin, and acetylcholine do undergo changes in their skin transudate levels after niacin challenge (Morrow *et al.*, 1992; Plummer *et al.*, 1977). However, Papaliodis *et al.* (2008) showed that niacin induced the release of serotonin from human platelets *in vitro* and elevated blood levels of serotonin after intraperitoneal injection of niacin in rats. Although further study will be needed to clarify the possible role of serotonin, the vast majority of evidence points to a strongly predominant role of AA metabolites as primary mediators of the flush response to niacin. Other eicosanoid vasodilators, however, have not been well studied in SZ.

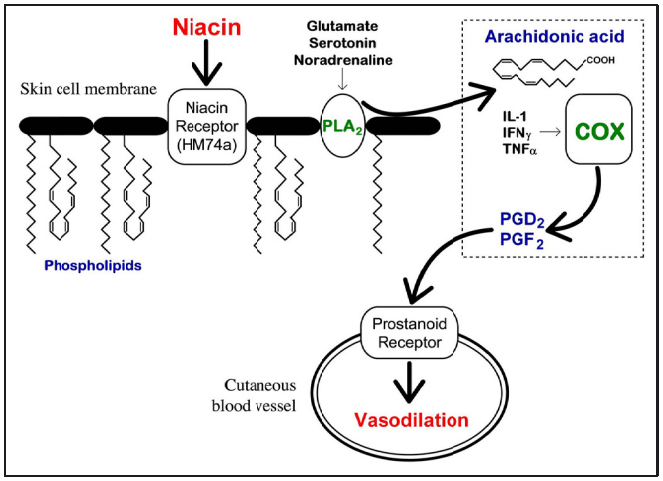

Fig. 3. The mechanism of niacin-induced skin flushing (adapted from Messamore *et al.*, 2010). Abbreviations: COX, cyclooxygenase; PLA_2, phospholipase A_2; IL, interleukin; INF, interferon; TNF, tumor necrosis factor; PGD_2, prostaglandin D_2; PGF_2 prostaglandin F_2.

7 Mechanism of the niacin flush response

A model of our current understanding of the mechanism of niacin-induced skin flushing is illustrated in Figure 3. Niacin interacts with a specific G-protein coupled receptor, HM74a, located on dermal macrophages and adipocytes (Benyó *et al.*, 2006; Urade *et al.*, 1989); its activation by niacin stimulates PLA_2mediated formation of AA (Tang *et al.*, 2006). Formation of AA is the rate-limiting step in the biosynthesis of the vasodilatory PGD_2 and E2 (PGE_2) (Murakami and Kudo 2004) These prostaglandins bind to specific prostanoid receptors on vascular smooth muscle within the skin. Activation of prostanoid receptors dilates cutaneous blood vessels (Lai *et al.*, 2007), and a visible skin flush arises from the ensuing increased blood flow (Benyó *et al.*, 2005; Maciejewski-Lenoir *et al.*, 2006; Morrow *et al.*, 1989, 1992).

8 The abnormal niacin response in SZ

Abrams Hoffer first reported observations that a substantial portion of patients with SZ are unusually resistant to the skin flush effect of pharmacologically-dosed niacin (Hoffer, 1962). Citing this work, and supporting these observations with clinical evidence of prostaglandin defects in the illness, Horrobin (1980a, 1980b) proposed that the niacin response abnormality could be used to demonstrate a prostaglandin signaling abnormality in SZ Abnormally attenuated skin flushing in response to niacin has been very widely replicated in samples of patients with SZ (Messamore, 2003; Smesny *et al.*, 2003; Yao *et al.*, 2015). The niacin response abnormality is consistently overrepresented in SZ compared to both healthy control groups (Messamore, 2003), or psychiatrically ill comparison groups with major depression (Bosveld-van Haandel *et al.*, 2006) or bipolar disorder (Liu *et al.*, 2007; Ross *et al.*, 2004; Yao *et al.*, 2015).

Consistent with the view that SZ is an etiologically heterogenous disorder, the niacin response abnormality is not present in all patients with SZ. The prevalence of the niacin abnormality was pegged at 80 to 90% in some studies (Puri *et al.*, 2001; Ward *et al.*, 1998). However, we have observed a prevalence of about 30% in SZ patients in two separate experiments, and 20% in first-degree relatives of patients with SZ (unpublished data). There has been very little consistency across reports with respect to the methods to stimulate or measure blood flow. This methodological variability accounts for the disparity of estimates of the prevalence of the niacin response abnormality in SZ. If, however, the same methods are used, there is remarkable consistency in the ability to find higher rates of abnormality among SZ patients *versus* other clinical or healthy comparison groups.

9 Biochemical correlates of abnormal niacin response

Lower RBC membrane AA levels are associated with decreased niacin sensitivity, but this expected correlation has only been described in a healthy control group (Messamore *et al.*, 2010). Although lower AA levels were found in patients who did not flush in response to oral niacin (Glen *et al.*, 1996), no correlation between AA levels and niacin response was observed in two different groups of patients with SZ (Maclean *et al.*, 2003; Messamore *et al.*, 2010). On the other hand, an unexpected correlation was observed between maximal niacin-induced blood flow and red blood cell membrane levels of adrenic acid (22:4 n-6), the elongation product of AA. Adrenic acid has vasodilatory actions in bovine coronary arteries and in arteries of the cortical layer of the adrenal gland (Kop *et al.*, 2010). Lack of correlation between AA levels and niacin response may result from a homeostatic imbalance within the n-6 PUFAs pathway in SZ. The significance of adrenic acid levels as they relate to niacin-induced blood flow response deserves further attention.

RBC membrane levels AA are normally tightly correlated with its immediate elongation product adrenic acid (22:4 n-6). However, this expected correlation is abolished in SZ (Messamore *et al.*, 2010). Similar precursor-product dysregulations have also shown in tryptophan (Yao *et al.*, 2010b) and purine (Yao *et al.*, 2010a) pathways. Although many of these correlated relationships persist across disease or medication status, others are lost among patients with SZ.

10 Clinical correlates of abnormal niacin response

The extent to which abnormal niacin-induced skin flushing associates with clinical manifestations of SZ has recently been reviewed (Messamore, 2012). Impaired niacin-induced flushing has been associated with greater severity of both positive and negative symptoms of SZ (Berger *et al.*, 2002; Glen *et al.*, 1996; Hudson *et al.*, 1997; Smesny *et al.*, 2003). Niacin response impairment was significantly linked to inorganic phosphate levels revealed by ^{31}P magnetic resonance spectroscopy (Puri *et al.*, 2007). This suggests that niacin-abnormal SZ patients may have higher levels of cerebral energy metabolism. Niacin response, as reflected in the 'volumetric niacin response

score' appears much more impaired among SZ patients with a history of violence (Puri *et al.*, 2007) compared to ordinary SZ patients (Puri *et al.*, 2002). Niacin response impairment is associated with worsened global functioning among patients with SZ (Messamore, 2012). Additionally, the niacin response abnormality is associated with significant cognitive impairment in SZ (Nilsson *et al.*, 2015).

11 The niacin response abnormality is not an artifact of medication or smoking status

Evidence suggests that neither antipsychotic drugs nor smoking significantly affect the niacin skin flush response (Mills *et al.* 1997; Shah *et al.* 2000; Smesny *et al.* 2001; Turenne *et al.* 2001). The niacin skin flush is not affected by local anesthetics, suggesting that local neurotransmitter release is not involved in niacin-induced vasodilatation (Winklemann *et al.*, 1965). There is no correlation between antipsychotic drug dose and niacin sensitivity in patients with SZ (Hudson *et al.*, 1997; Messamore, 2003). Neither has a significant difference in niacin sensitivity been found between medicated versus unmedicated patients (Shah *et al.*, 2000). In contrast, bipolar disorder patients who take antipsychotic medications have a normal or even enhanced flush response (Hudson *et al.*, 1997) Moreover, niacin subsensitivity occurs in first-degree relatives of schizophrenics, which suggests that this is a heritable trait, independent of medication status (Shah *et al.*, 1999; Waldo, 1999). On the other hand, Tavares *et al.* (2003) reported that 4 out of 13 SZ patients with niacin subsensitivity became sensitive to niacin after 8 weeks of atypical antipsychotic drug treatment. If such drugs do tend to normalize niacin sensitivity, then the potential bias in patient sample would be to underestimate the prevalence or magnitude of the niacin response abnormality in SZ. Taken together, comparing the niacin-induced flushing between medicated and unmedicated SZ patients, or unmedicated, non-psychotic relatives, suggests that the niacin response abnormality in SZ is not an artifact of antipsychotic medications (Chang *et al.*, 2009; Lin *et al.*, 2007; Maclean *et al.*, 2003; Shah *et al.*, 2000).

Similarly, it appears that nicotine use has no effect on the niacin-induced flushing response (Chang *et al.*, 2009; Liu *et al.*, 2007; Messamore, 2003, 2010; Ross *et al.*, 2004; Shah *et al.*, 2000; Smesny *et al.*, 2003). Our recent findings (Yao *et al.*, 2015) also support the notion that niacin sensitivity is not significantly affected by smoking.

12 Possible mechanisms for the niacin response abnormality in SZ

As depicted in Figure 3, there are several possible explanations for the finding of niacin subsensitivity in SZ. These include: abnormal signaling at the niacin receptor; abnormal presentation of free AA to COX; abnormal COX activity; abnormal conversion of initial COX products to vasodilatory end products; or abnormal signaling at prostanoid receptors in vascular smooth muscle. Support for abnormal niacin receptor signaling is provided by a report of decreased niacin receptor expression in postmortem brain from SZ patients (Miller and Dulay, 2008).

Presentation of free AA to COX is accomplished by the action of PLA_2, which may be abnormally active in niacin-subsensitive SZ (Hudson *et al.*, 1996; Tavares *et al.*, 2003). Any process leading to diminished output of prostaglandins could potentially account for niacin subsensitivity. Abnormal COX activity in SZ was indirectly demonstrated by Das and Khan (1998).

Cyclooxygenase action on AA initially produces prostaglandin H_2, which is subsequently converted by tissue-specific isomerases to vasodilatory end-products. Isomerase abnormalities have been detected in discrete brain regions from patients with a variety of mental illnesses (Maida *et al.*, 2006).

It is intriguing to note that none of these pathways is specifically targeted by existing antipsychotic medications. Discovering the mechanisms responsible for the niacin response abnormality may inform the development of novel treatment strategies. Such treatments would likely involve targets outside the traditional monoamine receptors and thus would be expected to augment the efficacy of current medications. Elucidating the mechanism of the niacin response abnormality may also lead to physiologically-informed categorization of mental illness.

13 Conclusions

There is a compelling need to categorize the schizophrenias according to physiological criteria. Ideally such physiologically-defined categories would lead more easily than the older, traditional schema to insights about biochemical or genetic causes – and would suggest more tailored and effective treatments. Although this goal is desirable, there have been relatively few leads as to which physiological abnormalities may be more promising to follow.

We suggest that the niacin skin flush response abnormality is a viable candidate for the physiological subtyping of SZ In contrast to the incompletely-understood etiology of SZ, the mechanism of niacin-induced skin flushing in man is relatively well-characterized. This detailed knowledge, coupled with the accessibility of skin for scientific study, presents a technically feasible, straightforward, and economically attractive opportunity to broaden our understanding of the biochemical changes that accompany SZ.

It is intriguing to note that none of the biochemical pathways mediating the niacin response is specifically targeted by existing antipsychotic medications. Discovering the mechanisms responsible for the niacin response abnormality may inform the development of novel treatment strategies. Such treatments would likely involve targets outside the traditional monoamine receptors and thus would be expected to augment the efficacy of current medications. As the metabolic and genetic underpinnings of this biomarker are elucidated, it should yield valuable insights into the complex pathophysiology of schizophrenic illness.

Disclosure

The authors declare no conflict of interest

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