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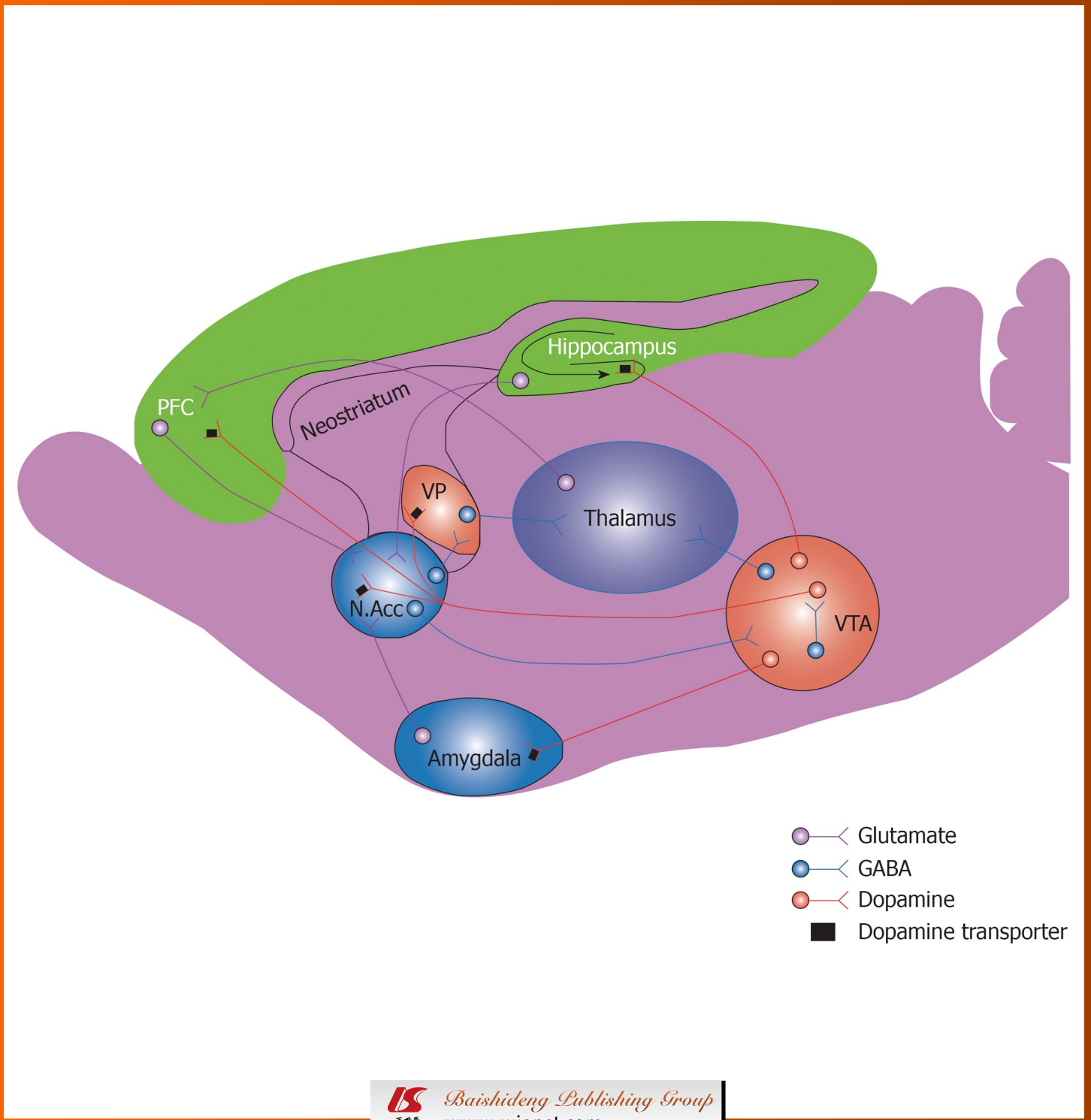

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EDITORIAL

Endocannabinoid system: A newer molecular target for the treatment of alcohol-related behaviors

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Abstract

The cannabinoid (CB) receptors, endocannabinoids (eCB) and their synthesizing and catabolizing enzymes and the proteins involved in their transport, constitute what is now recognized as the eCB system. The eCBs are a class of lipids that have been identified as retrograde messengers and produce their effects *via* presynaptic CB receptors. The major function of the eCBs has been suggested to be that of modulating the release of several neurotransmitters implicated in a number of biological functions that include reward and reinforcement. There is now significant evidence to suggest that the eCB system plays an important role in the development of alcohol tolerance, dependence and relapse. Recent studies suggest that the pharmacological manipulation of the eCB system has the potential not only to block the direct reinforcing properties of alcohol but also alleviate behavioral abnormalities associated with relapse. There is also accumulating evidence that points to the possible utility of the eCB system targeted drugs in the treatment of alcoholism-related behavioral disorders. The agents that block CB1 receptor function or inhibit the synthesis of eCBs are attractive candidate drugs that need to be explored. Further understanding of the role of the eCB system in molecular mechanism/s that underlies alcoholism-related behaviors should lead to a better treatment of this devastating disorder.

Key words: Endocannabinoids; CB1 receptor; Alcohol; Tolerance; Dependence

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INTRODUCTION

The endocannabinoid (eCB) system consists of cannabinoid (CB) receptors, eCBs, anandamide (AEA) and 2-arachidonyl glycerol (2-AG) and the enzymes involved in their synthesis, transport and degradation[1-4]. The eCBs mimic many of the pharmacological and behavioral effects of tetrahydrocannabinol (THC), a psychoactive component of marijuana and are considered as a new class of neuromodulators[5,6]. Unlike classical neurotrans-

mitters, eCBs are not stored in the vesicles but are released upon demand from membrane phospholipids of postsynaptic neurons[7]. The eCBs have been shown to act as retrograde messengers and regulate neurotransmitter release *via* binding to presynaptic CB1 receptors[8].

Alcoholism is a complex psychiatric disorder characterized by impaired control over drinking, leading to tolerance, physical dependence and relapse. The mechanisms underlying this disorder are poorly understood at the present time. Alcohol effects appear to be mediated through several intracellular signal transduction pathways involving many classical neurotransmitters and ion channels in different brain regions[9]. There is a growing body of evidence now suggesting a significant role for the eCB system in a number of alcohol-related behaviors that include voluntary alcohol consumption, alcohol tolerance and dependence and addiction to other drugs of abuse. Recent studies have also shown that the drugs targeted against the components of the eCB system may have therapeutic potential in the treatment of a variety of illnesses including drug and alcohol addiction.

The studies investigating the mechanisms underlying the addictive behavior mediated through eCB signaling have been the subject of intensive research. Our laboratory was the first to implicate the eCB system in the development of tolerance to alcohol. Since our first publication in 1998, there have been significant new developments in understanding the role of the eCB system in many of the alcohol-related behaviors. As discussed in the following section, several laboratories including ours have investigated CB1 receptor-mediated mechanisms in explaining the behavioral effects of alcohol that include tolerance and dependence, voluntary alcohol consumption, and fetal alcohol spectrum disorders.

ALCOHOL TOLERANCE AND DEPENDENCE

We have previously demonstrated: (1) a downregulation of CB1 receptors and CB1 receptor function in chronic alcohol exposed (alcohol tolerant) mouse synaptic plasma membranes[10,11]; and (2) an increase in the levels of the eCBs, AEA and 2-AG in chronic alcohol exposed neuronal cells in culture *in vitro*[12,13], and in the levels of AEA in chronic alcohol exposed mouse brain *in vivo*[14,15]. In addition, the CB1 receptor density and function were found to be significantly downregulated in the cortex, hippocampus, striatum and cerebellum of Swiss-Webster mice that were made alcohol tolerant following 72 h chronic continuous alcohol vapor exposure[15], which returned to normal level 24 h after withdrawal from alcohol[15]. Consistent with rodent studies, the levels of CB1 receptors, CB1 receptor-mediated G-protein signaling and fatty acid amide hydrolase (FAAH) activity were also found to be significantly lower in the postmortem ventral striatum of alcohol-dependent subjects compared to the control group[16].

It has also been demonstrated that co-administration of CB1 receptor antagonist SR141716A during chronic alcohol exposure significantly reduces severity of alcohol withdrawal-induced handling-induced convulsions (HIC) in both alcohol-preferring (AA) C57BL/6J (B6) and alcohol-avoiding DBA/2J (D2) mice[17]. We also have shown that the mice lacking CB1 receptor gene (CB1 KO) chronically exposed to alcohol had reduced HIC[17] consistent with the results reported by Racz *et al*[18]. Acute administration of SR141716A has also been shown to completely abolish the alcohol deprivation effect (ADE) and alcohol's motivational properties in AA sP rats[19-21]. The mice lacking FAAH (FAAH-KO), an enzyme that regulates brain AEA levels, has also been shown to display reduced severity of HIC following withdrawal from chronic continuous 72 h alcohol vapor exposure compared to WT littermates[22], while no differences were found in acute alcohol-induced HIC between FAAH KO and WT mice[23]. These studies strongly suggest that the eCB system plays a critical role in the development of tolerance to and dependence on alcohol.

eCB SYSTEM AND ALCOHOL CONSUMMATORY BEHAVIOR

Significant differences in both the density and function of brain CB1 receptors between AA B6 and alcohol-avoiding D2 mice have been reported[17,24,25]. There is also evidence suggesting that the genetic deletion or pharmacologic manipulation of CB1 receptors result in reduced alcohol consumption in rodent models[17,26-36]. For example, the mice lacking the CB1 receptor gene consume significantly less alcohol compared to their wild-type counterparts[17,26-31] similar to the effect produced by pharmacological antagonism of CB1 receptor[32-36]. On the other hand, administration of the agonists CP-55940 and WIN55212 has been shown to enhance alcohol intake in rodents[17,37,38], which was reversed by co-administration of the antagonist SR141716A[17,39]. The FAAH KO mice are severely impaired in their ability to degrade the eCB, AEA, and have been shown to have approximately 15-fold higher brain levels of AEA compared to WT mice[40]. These mice consume significantly more alcohol compared to WT mice[22,41] and these findings have been replicated by another group[23]. In a recent study, a comparison of the expression of the eCB-related genes in AA and alcohol non-preferring (ANA) rats revealed a decrease in the expression of FAAH activity in prefrontal cortex (PFC) of AA rats[42]. The association of impaired FAAH function with alcohol self-administration was further confirmed by the following observations: (1) SR141716A administration dose dependently suppressed self-administration in AA rats when given systemically or locally into PFC; and (2) intra-PFC injection of the competitive FAAH inhibitor URB597 increased alcohol self-administration in non-selected Wistar rats[42]. An increased vulnerability to drug and alcohol abuse in humans has also been suggested to be due to polymorphism in the FAAH gene and reduced FAAH expression and activity[43,44]. These studies suggest that the eCB system at least in part may play a role in many of the alcohol-related behaviors.

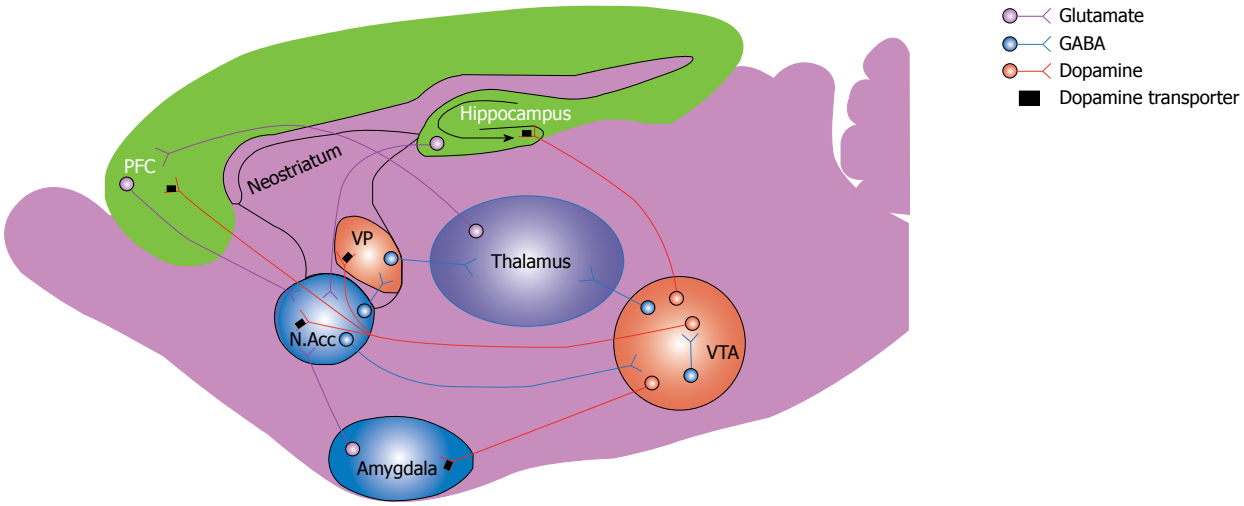

Figure 1 Limbic reward circuit. The diagram represents a reward circuitry in the rat brain. Highlighted are the nuclei representing the limbic structures of the basal forebrain including the amygdala, hippocampus, prefrontal cortex (PFC), nucleus accumbens (NAc), ventral pallidum (VP) and ventral tegmental area (VTA). Dopaminergic neurons in the VTA modulate information flow through the limbic circuit via projections to the NAc, amygdala, hippocampus, PFC and VP. Increase in the dopaminergic transmission in the limbic nuclei, particularly the NAc, may underlie the reinforcing effect of abused drug (Source: Sigma Aldrich).

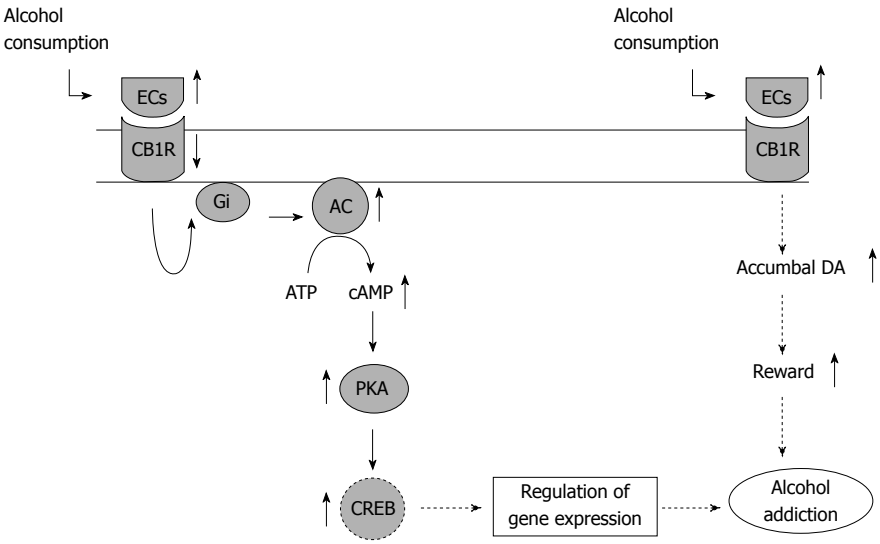

Figure 2 Possible mechanism of alcohol addiction involving the endocannabinoids system. Alcohol exposure has been shown to elevate endocannabinoids (eCBs). Repeated alcohol admistration downregulates the CB1 receptors as a neuroadaptation to elevation in the eCBs. This could lead to tolerance to alcohol. The desensitization of CB1 receptor-mediated G-protein coupling may reduce the inhibition of adenylate cyclase (AC) activity as CB1 receptors are negatively coupled to AC leading to increase in the CREB mediated gene expression. Modulation of other neurotransmitter systems by eCB system during alcohol exposure might also be associated with alcohol addiction. The mesocorticolimbic dopamine (DA) system represents a common neuronal substrate for reinforcing properties of drugs of abuse including alcohol. Chronic alcohol exposure-induced increase in AEA content appears to activate mesolimbic dopaminergic transmission by increasing the DA release in the shell of NAc. The functional interaction of the eCB system with DA system in reward-related brain regions might be associated with one of the underlying mechanisms of alcohol addiction. This figure is modified from our publication[3].

INTERACTION OF MESOLIMBIC DOPAMINERGIC AND eCB SYSTEMS; A POSSIBLE MECHANISM/S FOR DEVELOPMENT OF TOLERANCE TO AND DEPENDENCE ON ALCOHOL

The development of tolerance to and dependence on alcohol could be explained by possible interaction of the eCB system with the mesocorticolimbic system. The mesocorticolimbic dopamine (DA) system represents a common neuronal substrate for reinforcing properties of drugs of abuse including alcohol[45]. Dopaminergic projections originating from the ventral tegmental area (VTA) to the PFC and limbic structures that include nucleus accumbens (NAc) and amygdala have been suggested to play a critical role in reward and reinforcement. The CB1 receptors are present in most brain regions of the reward circuitry, including VTA, NAc, and in several other areas such as PFC, amygdala and hippocampus[46]. The DA neurons of the mesocorticolimbic system are

controlled by excitatory and inhibitory inputs that are modulated by CB1 receptors[47,48]. The final effect on the modulation of VTA dopaminergic activity by eCBs depends on the functional balance between the inhibitory GABAergic and excitatory glutamatergic inputs, both of which are inhibited by eCBs under different physiological conditions[47-49]. Alcohol consumption has been shown to increase AEA content in limbic forebrain[42], which appears to activate mesolimbic dopaminergic transmission by increasing the DA release in the shell of NAc[26]. As indicated earlier, a significant reduction in acute alcohol-induced DA release in the NAc shell has been reported in mice that lacked CB1 receptor gene similar to wild type mice treated with CB1 receptor antagonist[26]. It is of interest also to note that subchronic treatment with CB1 receptor agonist WIN-55,212-2 inhibited the release of DA in NAc of rats that were exposed chronically to alcohol[49]. An intravenous administration of both AEA and methandamide (a stable derivative of AEA) and pharmacologic inhibition of FAAH with URB597 led to increase in accumbal DA levels[50] (Figure 1).

The downregulation of CB1 receptors due to chronic alcohol exposure that results in tolerance to alcohol may be a compensatory neuroadaptation in response to elevation in the eCBs. This in turn might modulate the DA function in reward-related brain regions leading to alcohol addiction (Figure 2).

The dependence and relapse to alcohol may be due to an imbalance between excitatory glutamatergic and inhibitory GABAergic systems caused by altered CB1 receptor function. This could possibly be the result of altered eCB tone induced by chronic alcohol exposure. It is well documented that in the progression to alcohol tolerance and dependence, neuroadaptation occurs resulting in hypoactive GABA receptors and hyperactive NMDA receptors causing a hyperexcitable state that mediates both acute and protracted withdrawal states[45-48]. On the cessation of alcohol use, withdrawal symptoms occur most likely mediated by increased glutamate release. Relapse to alcohol use might reduce these effects and works *via* negative reinforcement to promote the addicted state[45-48]. These findings strongly implicate a role for the eCB system in reward and reinforcement properties of alcohol and the CB1 receptor targeted drugs should be exploited for future therapeutic drug development.

POTENTIAL THERAPEUTIC UTILITY OF DRUGS TARGETED AGAINST THE eCB SYSTEM IN THE TREATMENT ALCOHOLISM; CONCLUDING REMARKS

Despite significant developments in understanding of the neurobiological basis of alcohol tolerance and dependence, thus far no effective treatments are available to treat this devastating disorder. As evidenced in the foregoing discussion the eCB system appears to be a promising target with therapeutic potential. For example, CB1 receptor antagonist/inverse agonist SR141716A has been shown to reduce the development of tolerance to and dependence on alcohol in preclinical rodent models[15,18-20]. It has also been shown to reduce alcohol intake in AA rodents[17,21]. It is worth noting that two Phase Ⅱ clinical feasibility studies for the effectiveness of SR141716A (rimonabant), a CB1 receptor antagonist, on the prevention of alcohol relapse have been conducted in human alcoholics and found no significant improvement over the placebo patients[51]. In another clinical trial the rimonabant was found to have no effect on alcohol consumption in nontreatment-seeking heavy alcohol drinkers[52]. However, the rimonabant, due to incidence of severe adverse psychiatric side effects, FDA disapproved its commercialization. Nevertheless, further understanding of the neurobiological basis of alcohol abuse-related behaviors involving the components of the eCB system would reveal possible newer targets and future studies should focus on this aspect. Taken together, the available literature strongly support a role for the eCB system in alcohol-related behaviors and the CB1 receptor antagonists and drugs targeted to the eCB metabolizing enzymes are attractive candidates for the treatment of alcoholism.

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OBSERVATION

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Nicotinic acid: Do we know how it works after 55 years of clinical experience?

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Abstract

Nicotinic acid (NA) comprises the oldest hypolipidemic drug, in use since 1955. Despite its established broad spectrum effect on lipid profile and the associated reduction in cardiovascular morbidity and mortality, the mechanisms by which NA achieves its beneficial effects remain elusive. Regarding the NA-associated reduction in triglyceride and low density lipoprotein cholesterol levels, data are controversial. The prevailing view which suggested that NA inhibits lipolysis and decreases free fatty acid (FFA) release both *via* activation of adipose tissue G-protein receptor-109A (GPR109A) and *via* inhibition of hepatic triglyceride synthesis is currently debated by the observation that the initially decreased FFA levels rebound during long-term NA treatment even though the beneficial NA effects on lipid metabolism are preserved, while other mechanisms involving modulation of transcription and translation pathways are emerging. In addition, NA has been demonstrated to affect high density lipoprotein (HDL) particles remodeling in a number of ways, including reducing cholesterol ester transfer protein levels and activity, increasing apolipoprotein A-I levels, eliminating HDL hepatic uptake, increasing cholesterol efflux *via* ATP-binding cassette A1, inhibiting hepatic lipase, thereby overall increasing the plasma residence time of HDL and apoA-I with retention of cholesterol esters in HDL. Focus of this article is to present the mechanisms by which NA exerts its broad spectrum hypolipidemic actions.

Key words: Dyslipidemia; Nicotinic acid; Niacin; Mechanisms; GPR109A; Free fatty acids

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INTRODUCTION

Nicotinic acid (NA), also known as the water-soluble vitamin B3 (niacin), comprises the oldest hypolipidemic agent, being in use since 1955[1]. It decreases by 5%-25% and 20%-50% the levels of low density lipoprotein (LDL) cholesterol and triglycerides (TG), respectively, while NA remains the most effective currently available agent for raising high density lipoprotein (HDL) cholesterol levels (by 20%-25%) and decreasing the levels of lipoprotein (a) [Lp(a)] (by 28%-40%)[2,3]. Moreover, a number of clinical trials have demonstrated that NA may decrease cardiovascular events[4] and total mortality[5] in patients with coronary heart disease. Overall, NA comprises a hypolipidemic agent with unique broad-spectrum lipid-modifying properties and possible clinical benefits[6,7]. However, the mechanisms by which NA exerts its lipid-modifying

effects remain elusive. Focus of this paper is the presentation of these mechanisms. We searched PubMed up to 10 August 2011 using combinations of the following keywords: niacin, NA, mechanism, action, GPR109A, free fatty acids (FFA), dyslipidemia, hypolipidemic, liver, adipose tissue, macrophages and receptor. The references of these articles were scrutinized for relevant articles.

TG AND LDL CHOLESTEROL LEVEL REDUCTION

The mechanisms which contribute to the NA-associated TG and LDL cholesterol level reduction are not fully understood. However, the prevailing view holds that NA achieves TG and LDL cholesterol level reduction, primarily by affecting both adipose tissue's and liver's TG metabolism. (Figure 1).

NA's effect on adipose tissue

G-protein receptor-109A (GPR109A), also known as HM74A receptor in humans[8] is expressed in adipose tissue, spleen and immune cells[9-11]. NA binds and activates GPR109A in adipose tissue inducing a Gi-mediated inhibition of adenylyl cyclase activity, thereby resulting in a decrease of cyclic adenosine monophosphate (cAMP) intracellular levels[12]. This leads to decreased lipolysis, as cAMP is the main intracellular mediator of prolipolytic stimuli. cAMP normally activates protein kinase A (PKA) to phosphorylate various proteins, including perilipin and hormone-sensitive lipase (HSL), thereby promoting lipolysis[12]. The decrease in circulating FFA results in a substrate shortage for hepatic very low density lipoprotein (VLDL) production, consequently reducing plasma levels of LDL cholesterol and TG[13,14]. Paradoxically, it has been established that the initially decreased FFA levels rebound during long-term NA treatment even though the beneficial NA effects on lipid metabolism are preserved[15,16]. But how that happens? Phosphoenolopyruvate carboxykinase (PEPCK1) is a key enzyme in adipose tissue gluconeogenesis and its deficit leads to increased FFA release Recently, NA was associated with decreased expression of PEPCK1 in adipose tissue and thus increased FFA release, partly explaining the rebound phenomenon[17]. Another contributing mechanism to FFA rebound could also be the NA-induced up-regulation of tumor necrosis factor-α (TNF-α) transcription and the consequent increase of interleukin-6 (IL-6), as both of them comprise cytokines with lipolytic properties, thereby increasing FFA release[17]. Of note, MK-0354, a partial agonist of GPR109A which resulted in decreased plasma FFA concentrations, paradoxically failed to affect LDL cholesterol and TG levels[18]. Overall, it seems that the contribution of GPR109A activation to the long-term hypolipidemic effects of NA remains debatable.

NA's effect on liver

NA has been demonstrated to inhibit diacylglycerol acyl transferase 2 (DGAT2) which comprises a key enzyme

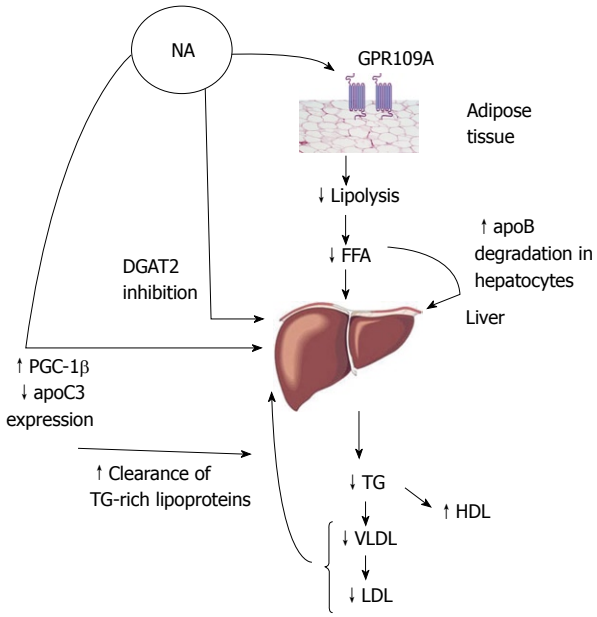

Figure 1 How nicotinic acid decreases triglycerides and low density lipoprotein cholesterol levels. NA: Nicotinic acid, TG: Triglycerides, LDL: Low density lipoprotein; FFA: Free fatty acids; VLDL: Very low density lipoprotein; DGAT2: Diacylglycerol acyl transferase 2; PGC-1β: Peroxisome proliferator-activated receptor γ coactivator-1β; apoC3: Apolipoprotein C3; apoB: Apolipoprotein B.

for the hepatic TG synthesis[19]. However, DGAT2 inhibition has been observed at NA concentrations 100-folder higher than those associated with maximal pharmacological effects of NA on FFA and TG levels[20].

Current evidence indicates that the post-translational apolipoprotein B (apoB) degradative processes regulate the hepatic assembly and secretion of VLDL and the subsequent generation of LDL particles. The availability of TG for the addition to apoB during intracellular processing appears to play a central role in targeting apoB for either intracellular degradation or assembly and secretion as VLDL particles. NA-induced TG synthesis inhibition has been demonstrated to create a favorable environment for protease-mediated intracellular apoB degradation in hepatocytes, thereby resulting in decreased apoB-containing VLDL and thus LDL particle formation[21,22]. In addition, stable isotope methodologies in dyslipidemic patients demonstrated NA-enhanced plasma clearance of TG-rich lipoproteins containing either apoB100 or apoB48, thereby implying that NA may affect both hepatic and intestinal TG-rich lipoproteins' metabolism[22]. Of note, NA failed to interact with hepatic LDL-receptors[23].

Further actions on TGs have been associated with the NA-induced inhibition of peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1β (PGC-1β). PGC-1β is a transcriptional co-activator that is regulated by FFA. Specifically, PGC-1β induces hypertriglyceridemia in response to dietary fats through activation of hepatic lipogenesis and lipoprotein secretion. Moreover, PGC-1β regulates plasma TG levels by stimulating apolipoprotein C3 (apoC3) expression, thereby inhibiting

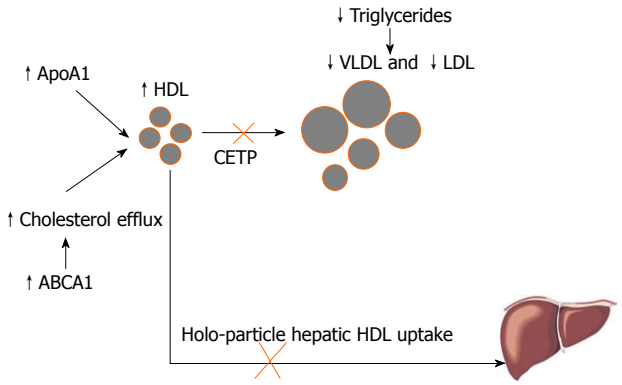

Figure 2 How nicotinic acid can increase high density lipoprotein cholesterol level. NA: Nicotinic acid; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; CETP: Cholesterol ester transfer protein; ApoA1: Apolipoprotein A1; ABCA1: ATP-binding cassette protein A1.

apolipoprotein E (apoE) driven clearance of TG-rich lipoproteins[24]. Of note, both acute and chronic treatment with NA were associated with reduced hepatic expression of PGC-1β and apoC3, while knockdown of PGC-1β or APOC3 in mice liver recapitulated NA's hypolipidemic effect[24].

HDL CHOLESTEROL LEVEL ELEVATION

The mechanisms by which NA elevates HDL cholesterol level have not been fully elucidated. However, a number of mechanisms have been shown to contribute to the observed NA-induced HDL cholesterol level elevation. (Figure 2).

NA's effect on cholesterol ester transfer protein

The NA-induced decrease in TG levels in apoB-containing lipoproteins (LDL and VLDL) eliminates the exchange of TG for cholesteryl-esters from HDL particles mediated by cholesterol ester transfer protein (CETP), resulting in increased HDL concentration[25,26]. In fact, NA-associated HDL cholesterol elevation depended on the presence of CETP in mice[27]. However, the partial GPR109A agonist MK-0354 failed to raise HDL levels despite the reduction in plasma FFA[18]. NA has been also associated with reduced CETP activity per se as a result of reduced hepatic CETP gene expression and reduced release of CETP in plasma[28]. Of note, the reduction in CETP activity can also explain how NA promotes the maturation of HDL into large particles[22].

NA's effect on the holo-particle uptake pathway

NA has been associated with reduced hepatic uptake of HDL, potentially by the holo-particle uptake pathway. In fact, NA has been shown to inhibit the surface-expressed ATP-synthase β-chain which acts as a HDL holoparticle receptor leading to slower HDL catabolism[29].

NA's effect on apolipoprotein A-I metabolism

Data regarding the effect of NA on apolipoprotein A-I (apoA-I) metabolism are controversial. NA has been shown to increase production rate of apoA-I both in liver and intestinal cells[22,30]. In fact, NA activates both mitogen activated protein (MAP) kinase and the PPAR transcription factors pathways, which both affect hepatic apoA-I production[31-33]. On the contrary, other studies with hepatic cells and mice reported no effect of NA on apoA-I production rate, while NA administration was associated with decreased apoA-I hepatic removal[28,34].

NA's effect on ATP-binding cassette protein A1

NA, potentially *via* GPR109A activation, enhances transcription of cholesterol efflux transporters ATP-binding cassette protein A1 and G1 (ABCA1 and ABCG1, respectively). Thus, NA-induced cholesterol efflux from macrophages could also contribute to the reported increase in HDL cholesterol levels[23,35]. Moreover, NA dose-dependently stimulated PPARγ and ABCA1 expression and promoted ApoA-I-induced cholesterol efflux in adipocytes. In fact, treatment of PPARγ-selective antagonist GW9662 significantly abolished the NA-induced increase in ABCA1 mRNA expression and cholesterol efflux to ApoA-I[36]. Of note, NA had no effect in HDL cholesterol levels in GPR109A knock-out mice[36]. On the other hand, overexpression of GPR109A reduced hepatocyte ABCA1 expression and activity, thereby decreasing cholesterol efflux to nascent apoA-I and reducing HDL cholesterol levels in mice[37]. Overall, it seems that NA effect on ABCA1 is mediated *via* GPR109A and we can speculate that a phenomenon of tachyphylaxis may occur in case of GPR109A overstimulation.

NA's effect on hepatic lipase

In mice NA has been shown to inhibit hepatic lipase activity. This results in decreased remodeling of plasma HDL, thereby limiting HDL clearance[28].

Lp(a) REDUCTION

No particular mechanisms regarding the NA-induced reduction of Lp(a) have been reported. However, the NA-associated reduction in the circulating FFA by both GPR109A-mediated lipolysis and DGAT2 inhibition results in reduced VLDL and subsequently LDL levels[13,19]. As LDL particles comprise the substrate for Lp(a) it comes as no surprise that NA also reduces Lp(a) levels.

CONCLUSION

Overall, NA exerts broad spectrum effects on lipids through a number of elusive and even controversial mechanisms. Regarding the NA-associated reduction in TG and LDL cholesterol levels, the prevailing view which suggested that NA inhibits lipolysis *via* GPR109A activation is currently debated by both the rebound phenomenon and the failure of partial GPR109A agonist, MK-0354 to reduce TG and LDL cholesterol levels despite the decrease in plasma FFA. On the other hand,

the NA-associated DGAT2 inhibition was reported at NA levels much higher than those used in clinical setting. However, it can be argued that plasma levels of NA may not reflect its bioavailability at the liver. In addition, PGC-1β mediated increased clearance of TG-rich lipoproteins may also contribute to hypolipidemic effects of NA.

Similarly, data regarding the mechanisms by which NA increases HDL cholesterol level are scant. However, it seems that NA affects HDL particles remodeling in a number of ways, including reducing CETP levels and activity, increasing apoA-I levels, eliminating HDL hepatic uptake, increasing cholesterol efflux *via* ABCA1, inhibiting hepatic lipase, thereby overall increasing the plasma residence time of HDL and apoA-I with retention of cholesterol esters in HDL.

Conclusively, the mechanisms by which the oldest hypolipidemic drug exerts its lipid-modifying effects remain elusive even after 55 years of clinical experience. However, it is undebatable that NA targets a number of different receptors expressed in a variety of cells including hepatic, intestinal and adipose tissue cells in order to achieve its broad spectrum effect on lipid profile. More research effort especially with genetically modified animals which do not express or overexpress a number of receptors or transporters including GPR109A, ABCA1, PGC-1β is needed in order to decode how NA really works.

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

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