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Diabetes & its Complications

Metadichol ® A Novel Nano Lipid; GPR 120 Agonist

Raghavan P.R*

Nanorx Inc, PO Box 131, Chappaqua, NY 10514, US.

***Correspondence:**
PR Raghavan, Founder and CEO, Nanorx Inc, Chappaqua, NY, USA, Tel: (914) 671-0224; E-mail: raghavan@nanorxinc.com.

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ABSTRACT

Metadichol® is a Nanoemulsion of long-chain alcohols found in many foods. Metadichol acts as an inverse agonist on Nuclear Vitamin D receptors (VDR) that have a ubiquitous presence in cells and acts by modulating the immune system and affects many biological processes to modulate many diseases.

We have demonstrated that Metadichol is useful in both type 1 and 2 diabetes and in modulating insulin levels and reducing sugar levels and thus increasing insulin sensitivity. We had earlier shown that it binds to VDR and thus an effect on glucose homeostasis that is a hallmark of VDR pathways. We now report also that it is an agonist of GPR120 (G protein-coupled receptor 120) which has emerged as a key target for metabolic diseases like obesity and insulin resistance.

In the in-vitro assay, Metadichol is comparable to GW9508 the most extensively used standard compound in GPR 120 research.

Keywords

Metadichol, VDR, Nuclear receptors, Inverse agonists, Protean agonists, GPR 120, FFAR4, Lipids, Insulin Resistance, Insulin sensitivity, Type 1 and Type 2 diabetes, Network biology, Multiple receptors targeting, BCAT1, PPARG.

Introduction

Diabetes is rampant across the world and was the cause of 4.6 million deaths in 2011. By the year 2030, over 450 million people will be affected [1].

Lifestyle disease modification like diet control can help in preventing Type two diabetes. Many experimental drugs are in various phases of development, but despite new insights into the mechanism of the disease, as of today, no effective solution is in sight.

Increasingly research has been that focussed on the superfamily of GPCRs and there are over 800, seven-transmembrane receptors that display different physiological and pathological functions [2]. Free fatty acids (FFAs) are known to act in regulating physiological functions through G-protein-coupled receptors the most important being GPR-120, also known as FFAR4, which is now an important therapeutic target against diabetes [3].

GPR120 have a ubiquitous presence in various tissues and cells [4]. GPR120 has functions in the homeostatic regulation of systemic metabolism and inflammation depending on this different tissue distribution. GPR120 activation can lead to positive effects on type 2 diabetes. GPR120 signals via both β- arrestin 2 and G proteins in the reported studies. GPR120 is an emerging target in the field of metabolic diseases.

Experimental

The GPCR assay was carried out by DiscoverRX, CA USA using PathHunter® assays which use adapted β-galactosidase complementation system. Enzyme Fragment Complementation (EFC) with β-galactosidase (β-Gal) as the functional reporter. In the PathHunter® β-Arrestin assay. The GPCR assays are the whole cell, functional tests that directly measure activity by detecting the interaction of β-Arrestin with the activated GPCR. It monitors the activation of a GPCR in a homogenous, non-imaging assay format. The enzyme is split into two inactive complementary portions: a small peptide called ProLink™ (PK) and a larger protein, called Enzyme Acceptor (EA). PK and EA are then expressed as fusion proteins in the cell, with PK fused to the GPCR of in-terest, and

EA fused to β-Arrestin. When the target GPCR is activated, and β-Arrestin recruited to the receptor, PK, and EA complementation occurs, restoring β-Galactosidase activity which is measured using chemilumi-nescent PathHunter® Detection Reagents. GW9508, a known GPR 120 agonist, was used as the standard.

Cell Handling

- PathHunter® cell lines were thawed from freezer stocks according to standard procedures.
- Cells were seeded in a total volume of 20 µL into white-walled, 384-well microplates and incubated at 37°C for a stipulated time before testing.

Agonist Format

- For agonist determination, cells were incubated with the sample to induce the response.
- Intermediate dilution of samples was carried out to obtain the 5X samples required in assay buffer
- five µL of 5X sample was added to cells and incubated at 37°C or room temperature for 90 or 180 minutes. Fi-nal test vehicle concentration was 1%.

Signal Detection

- Assay signal generated through a single addition of 12.5 or 15 µL (50% v/v) of PathHunter agent for detection followed by one-hour incubation at room temperature.
- Microplates were then read following signal generation with a Perkin Elmer EnvisionTM instrument for chemi-luminescent signal detection.

Data Analysis

- Compound activity was analyzed using CBIS data analysis suite (ChemInnovation, CA).
- For agonist mode assays, percentage activity was calculated using as follows;

% Activity =100% x (mean RLU of test sample — mean RLU of vehicle control) / (mean MAX control ligand — mean RLU of vehicle control).

Agonist assays, data was normalized to the maximal and minimal response observed in the presence of control ligand and vehicle.

Summary of Results

Table 1 shows the summary of results. Table 2 and 2-1 show the raw data, and Figure 1 shows the graphs of the agonist activity. Metadichol has the same response as the known GPR120 agonist GW9508.

Table 1

Compound Name	Assay Name	Assay Format	Assay Target	EC50 (ug/mL)	Slope	Curve Bottom	Curve Top	Max Response
Metadichol	Arrestin	Agonist	GPR120	3.3141	1.48	-4.1	105	105.3
GW9508	Arrestin	Agonist	GPR120	3.478	1.03	-5.5	105	101.68

Table 2

	Well ID	Concentration	Raw Value	Percent Efficacy
Metadichol	E21	0.048828	16800	-6.3995
	E22	0.048828	16000	-8.468
	E19	0.097656	17000	-5.8824
	E20	0.097656	17600	-4.331
	E17	0.19531	16800	-6.3995
	E18	0.19531	17000	-5.8824
	E15	0.39063	21000	4.4602
	E16	0.39063	19000	-0.71105
	E13	0.78125	23000	9.6315
	E14	0.78125	22800	9.1144
	E11	1.5625	29800	27.214
	E12	1.5625	27600	21.526
	E9	3.125	38200	48.933
	E10	3.125	36800	45.314
	E7	6.25	48000	74.273
	E8	6.25	45000	66.516
	E5	12.5	56200	95.475
	E6	12.5	55400	93.407
	E3	25	62000	110.47
	E4	25	58000	100.13

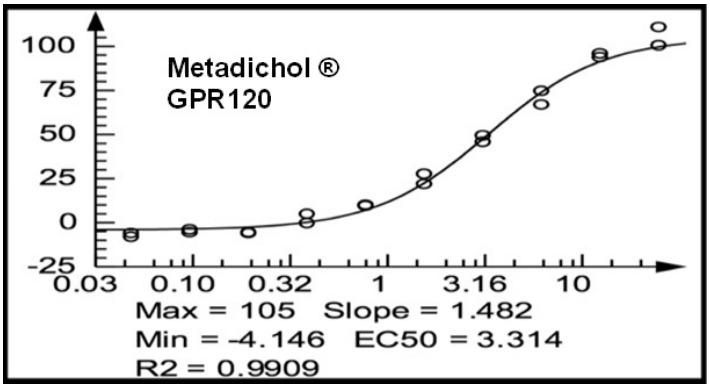
	Well ID	Concentration	Raw Value	Percent Efficacy
GW6506	A21	0.0050805	16200	-7.9509
	A22	0.0050805	18400	-2.2624
	A19	0.015242	16000	-8.468
	A20	0.015242	16600	-6.9166
	A17	0.045725	17000	-5.8824
	A18	0.045725	18800	-1.2282
	A15	0.13717	18800	-1.2282
	A16	0.13717	18200	-2.7796
	A13	0.41152	22600	8.5973
	A14	0.41152	21200	4.9774
	A11	1.2346	27400	21.008
	A12	1.2346	27800	22.043
	A9	3.7037	40800	55.656
	A10	3.7037	39000	51.002
	A7	11.111	49400	77.893
	A8	11.111	48000	74.273
	A5	33.333	55600	93.924
	A6	33.333	59000	102.71
	A3	100	61000	107.89
	A4	100	56200	95.475

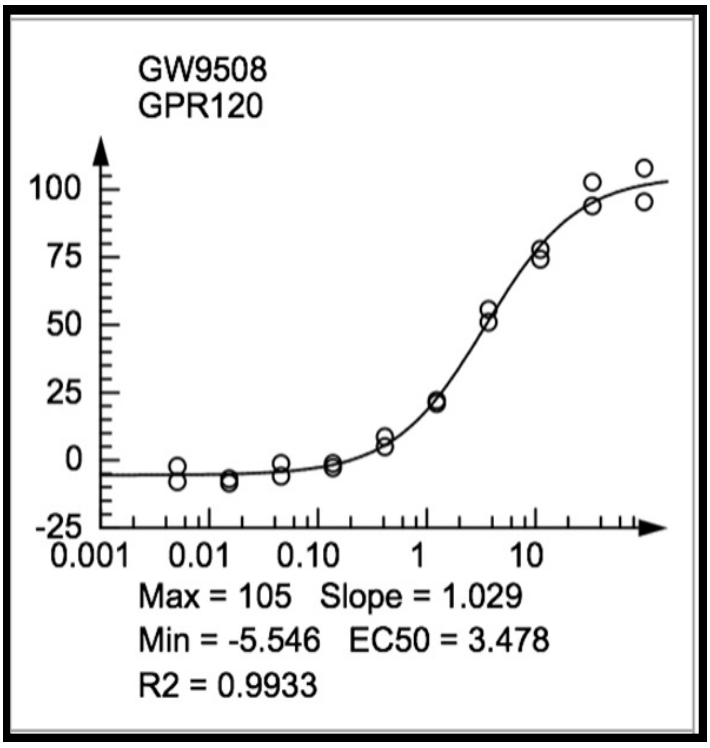
Discussion

Metadichol ® is a Nanoemulsion in water and has a particle size of less than 60 nm. Its mechanism of action is through its binding to the vitamin D receptor (VDR) as an inverse agonist [5].

The natural ligand for the VDR is 1,25-Dihydroxy Vitamin D is and acts as an agonist. Metadichol can act as both positive or as

negative agonists on the same receptor a property characteristic of protean agonist [6,7]. In the absence of constitutive activity, it behaves as an active agonist. If constitutive activity is present, it acts as an inverse agonist. Metadichol can reduce or increase insulin secretion [5,8].





For the functioning of the skeletal system [9], Vitamin D is very critical for the regulation of the immune system [9]. It has a vital role not only in controlling insulin synthesis and secretion as well [10,11]. Metadichol in addi-tion to binding with VDR also binds to other nuclear receptors that include PPAR Gamma [12].

Flawed metabolism of Branched Chain Amino Acid (BCAA) is associated with many chronic conditions like type II diabetes and other childhood disorders [13]. Metformin has been shown to in-hibit expression of mitochondrial branched-chain aminotransfer-ase (BCAT) [14]. We have recently shown that Metadichol is a potent inhibitor of BCAT1 [15].

The Agonism exhibited by Metadichol in GPR 120 assays show that it is acting on more than one target, VDR, BCAT1, has been shown previously. The current research approach that of a lock (receptor) and key (drug). The search to mitigate the side effects of drugs by looking for high selective ligands and has proven to be cost and time consuming without any in many ways a failure. Useful drugs act via pathways in targeting multiple proteins rather than single targets. Protein kinase inhibitors like Sutent and Gleevec, have demonstrated that their anticancer actions are due to their effects on multiple kinases [16].

Yıldırım, M.A, et.al suggest that there are many keys open a lock but the goal of drug discovery is to have a single key to open many locks, i.e., act via multiple pathways [17]. A practical approach for mitigating disease states may require multiple activities to be efficacious, together with the observation that perturbs biological networks is more important than individual targets [18].

Previously we have published case studies of Metadichol ® in Type 1 diabetes and type 2 diabetes patients [8,19]. It appears to be more efficient than many drugs on the market as it works multiple pathways on multiple receptor targets. Metadichol acts at the nuclear receptor level (VDR) and the transmembrane level (GPR120) and the Cytoplasm and mitochondrial level (inhibition of BCAT1) is probably what makes it such a powerful treatment of choice in diabetes relate diseases.

Conclusion

Metadichol has the potential to serve in mitigating diabetes with a broad spectrum of activity and with a safety that with no toxicity at doses of up to 5000 mg/kg [20-22]. Metadichol is a a far effective substitute to prescrip-tion drugs, which have been largely ineffective in diabetes and have many side effects that add to health care costs.

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