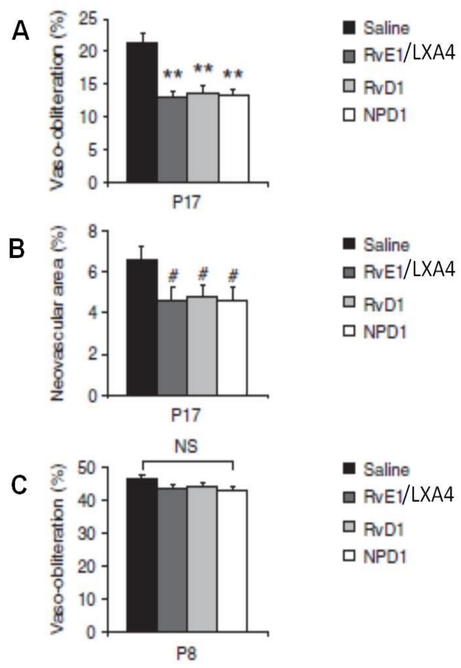
Small molecule lipid (SURYA-101) as a potential drug to prevent and manage diabetic retinopathy (DR)

Undurti N Das

UND Life Sciences, 2020 S 360th St, # K-202, Federal Way, WA 98003, USA

DR is a common cause of significant vision loss and blindness. Yet, there is no effective therapeutic intervention available for its prevention and management. SURYA-101, a lipid based small molecule that has potent anti-inflammatory and immunomodulatory actions is being developed as a potential drug for DR. It also has the potential to treat AMD (age-related macular degeneration) and retinopathy of prematurity.

SURYA-101 counteracts H_2O_2/tumor necrosis factor-α (TNF-α)/oxidative stress-triggered apoptosis of retinal pigment epithelial (RPE) cells, inhibits caspase-3 activation and IL-1β-stimulated expression of COX-2 (cyclo-oxygenase). In addition, studies revealed that n-3-polyunsaturated fatty acids (PUFAs)-derived neuroprotectin D1, resolvin D1 and resolvin E1 and arachidonic acid (AA)-derived lipoxin A4 (LXA4) protect against neovascularization by suppressing TNF-α (Figure 1). It is noteworthy that TNF-α is not increased in human DR both in the serum and vitreal fluid as shown in Tables 1 and 2 in our study. In contrast, both serum and vitreal IL-6 were increased in DR.



	Control (n = 26)	Diabetic (n = 25)	NPDR (n = 25)	PDR (n = 25)
IFN-γ (pg/mL)	3.21 ± 1.85	3.27 ± 2.19	5.31 ± 11.2	3.36 ± 1.66
TNF-α (pg/mL)	1.43 ± 0.85	1.47 ± 0.81	1.24 ± 0.51	1.73 ± 1.22
IL-10 (pg/mL)	1.67 ± 0.67	2.55 ± 1.78	1.93 ± 0.89	2.43 ± 1.03
IL-6 (pg/mL)	3.06 ± 1.67	3.98 ± 3.06	4.86 ± 2.95 * ↑	6.66 ± 4.78 * ↑
IL-4 (pg/mL)	2.27 ± 1.15	1.82 ± 0.73	1.29 ± 0.56	1.92 ± 0.88
IL-2 (pg/mL)	1.82 ± 1.08	2.48 ± 1.37	1.64 ± 0.94	2.16 ± 1.63

Values are expressed as mean ± SD.
* p < 0.05: control vs respective group.

Table 1. Serum cytokines in control, type 2 DM and DR groups. PDR = Proliferative DR.

Vitreous Parameter	Macular Hole (n = 20)	PDR (n = 30)
IFN-γ (pg/mL)	4.51 ± 2.39	4.92 ± 1.48
TNF-α (pg/mL)	2.62 ± 1.24	3.19 ± 0.9
IL-10 (pg/mL)	2.43 ± 1.0	3.33 ± 0.68 * ↑
IL-6 (pg/mL)	21.34 ± 35.95	291.09 ± 537.08 * ↑
IL-4 (pg/mL)	2.97 ± 1.34	2.82 ± 1.14
IL-2 (pg/mL)	2.08 ± 0.75	2.90 ± 1.05

Values are means ± SD.
* p < 0.05; comparison between respective group vs control.

Table 2. Cytokines in vitreal fluid

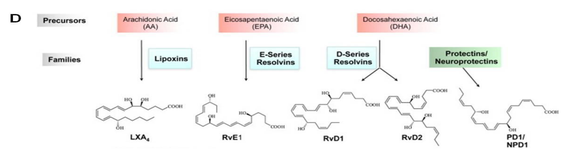


Figure 1. Vaso-obliteration at postnatal (P) 17 day in LXA4, RvD1, RvE1 or NPD1-treated mice compared with vehicle treated control. **A.** Vaso-obliteration at P17 in LXA4, RvD1, RvE1 or NPD1-treated mice compared with vehicle-treated control. B. Neovascularization at P17 in mice injected i.p. from P5-P8 with RvD1 (n =14), RvE1 (n =10) or NPD1 (n=14) compared with that in saline-treated mice (n=14). **C.** Vaso-obliteration at P8 with RvD1 (n=7), RvE1 (n=9), NPD1 (n=7) treatment. RvD1 = Resolvin D1 derived from DHA; RvE1 = Resolvin E1 derived from EPA; NPD1 = Neuroprotectin or Protectin D1 derived from DHA and LXA4 derived from AA. **D.** Formation of resolvins and protectins from EPA and DHA respectively. DHA also gives rise to resolvin D1 (RvD1).

In an extension of this study, we also observed that both plasma and vitreal LXA4 and brain-derived neurotropic factor (BDNF) levels are low in patients with DR compared to control as shown in Tables 3 and 4.

	Control (n = 27)	Diabetic (n = 27)	NPDR (n = 30)	PDR (n = 30)
BDNF (pg/mL)	73.45 ± 32.3	63.65 ± 30.07	47.51 ± 25.37 * ↓	45.86 ± 52.36 * ↓
LXA_4 (pg/mL)	127.95 ± 108.2	84.54 ± 99.62	60.51 ± 51.70 *	50.27 ± 41.17 *
VEGF (pg/mL)	960.09 ± 876.6	660.41 ± 446.25	580.16 ± 422.26	960.09 ± 876.6
PEDF (μg/mL)	4.17 ± 2.17	4.97 ± 2.83	5.73 ± 2.57	5.76 ± 3.34

Values are expressed as mean ± SD.
* p < 0.05: control vs respective group (Mann-Whitney U test).

Vitreous Parameter	Macular Hole (n = 18)	PDR (n = 27)
BDNF (pg/mL)	50.44 ± 79.14	13.47 ± 28.56 * ↓
LXA_4 (pg/mL)	54.45 ± 40.45	25.63 ± 23.1 *
VEGF (pg/mL)	33.78 ± 29.24	971.75 ± 951.03 *
PEDF (μg/mL)	3.38 ± 3.66	7.98 ± 4.26 *
VEGF/PEDF ratio	85 ± 143.20	165 ± 194.79

Values are expressed as mean ± SD . iabetic retinopathy and macular hole.*P < 0.05 control vs respective group.

Thus, LXA4 enhanced the production of BDNF, a well known neuroprotective molecule.

In animal models of type 1 and type 2 DM and subjects with diabetes mellitus, plasma phospholipid content of AA and docosahexaenoic acid (DHA) were found to be low (Table 5). Thus, low levels of LXA4 seen in plasma and vitreal fluid of DR could be due to AA (the precursor of LXA4) deficiency.

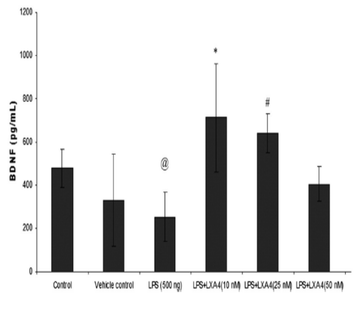


Figure 5. BDNF, a neuroprotective molecule, levels in LXA4 exposure on LPS-induced retinal pigment epithelial cells ARPE 19 in vitro. All values mean ± SD. @P<0.05; control vs LPS, *P<0.05; LPS vs LPS + LXA4 (10 nmol/L), #P<0.05; LPS vs LPS + LXA4 (25 nmol/L).

Fatty acid	Control (n=20)	Type 2 DM (n=10)
DGLA (20:3 n-6)	3.4 ± 1.0	1.7 ± 1.0*
AA (20:4 n-6)	9.4 ± 1.8	4.6 ± 1.8*
EPA (20:6 n-3)	0.4 ± 0.4	0.3 ± 0.3
DHA (22:6 n-3)	1.4 ± 0.5	0.5 ± 0.4*

Table 5. The percentage distribution of fatty acids from plasma phospholipid fraction in patients with type 2 DM. All values are expressed as mean ± S.D. *P<0.05 compared to control.

It is noteworthy that VEGF levels were found to be increased both in the plasma and vitreal fluid in those with DR. (i) LXA4 inhibited alloxan and other chemicals-induced apoptosis (Figure 2B). (ii) LXA4 restored LPS-induced suppression of BDNF levels to normal (Figure 3). (iii) LXA4 suppressed NF-κB and enhanced IKB expression (Figure 4). Furthermore, LXA4 inhibited free radical generation, TNF-α and IL-6 production, and suppressed COX-2, VEGF, and iNOS genes expressions. Hence, LXA4 is useful in the prevention and management of diabetic macular edema, DR and PDR. Resolvins, and protectins also showed actions similar to LXA4.

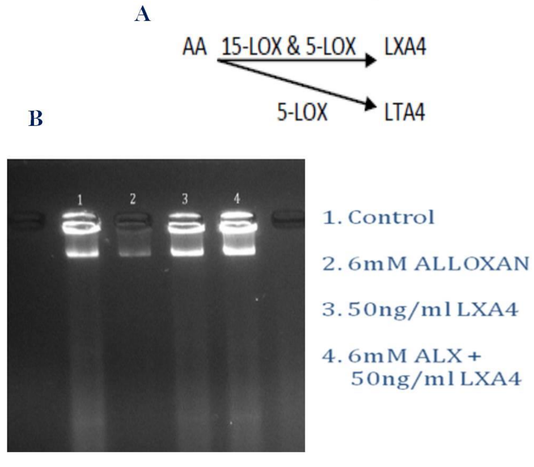


Fig. 2. A) Conversion of AA to LXA4 and LTA4.
B) Apoptosis prevention of RIN cells pre-treated with Lipoxin A4 followed by alloxan treatment

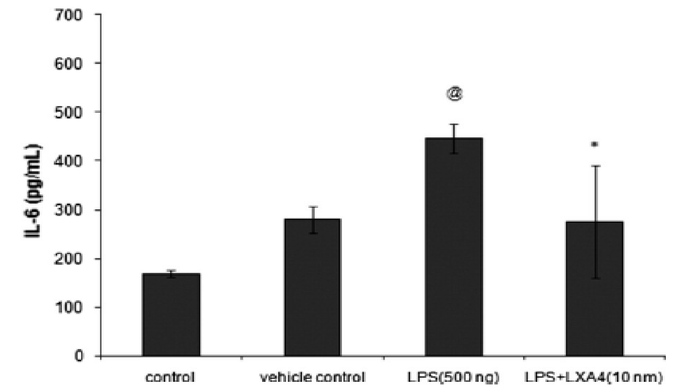
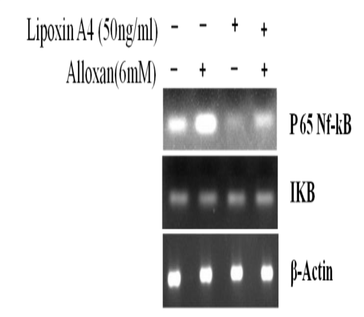


Figure 3. IL-6 levels enhanced by LPS decreased by LXA4 in retinal pigment epithelial cells decreased by LXA4.



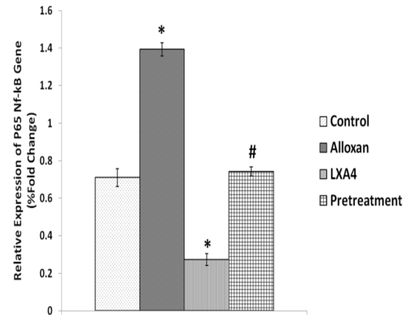


Figure 4. Expression of P65 NF-kB and IKB genes in LXA4 and alloxan-treated RIN cells. LXA4 decreased NF-kB but enhanced IKB expression and thus, suppresses inflammation and TNF-α production. *P < 0.05 compared to control; #P < 0.05 compared to alloxan control.

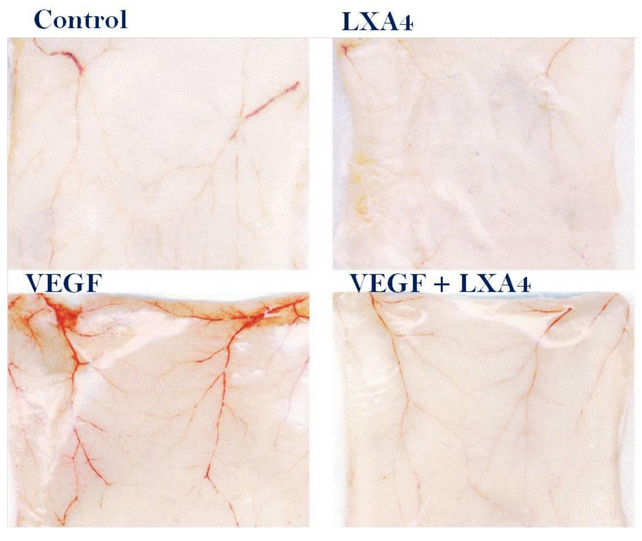


Figure 6. LXA4 inhibits VEGF-induced angiogenesis. LXA4 dose 10μg; VEGF dose 1μg.

Potential advantages and disadvantages

The existing product anti-VEGF antibody is the competitor. Unlike anti-VEGF antibody that only neutralizes VEGF, SURYA-101 inhibits VEGF production and enhances BDNF production, a neuroprotective molecule. Thus, SURYA-101 has cytoprotective, neuroprotective, anti-inflammatory and immunomodulatory actions and hence, is superior to anti-VEGF antibody.

Anticipated medical risks/safety of the device.

None anticipated based on current evidence except those associated with any intravitreal injection.

Describe the technologies employed in this device and the proof of concept to-date, and the current status of development.

Diabetes –related blindness costs the United States approximately $ 500 million annually. If SURYA-101 is approved for the treatment of DR, we anticipate that at least 50% of the market share will be for this product in view of its efficacy, multi-pronged action and unlikely to have significant side effects in view of its lipid nature and as retina is rich in lipids. Proof of concept data has been presented above.

Currently we are performing pre-clinical toxicity studies.

Inference:

It is evident from the results obtained so far that LXA4, protectin D1 and (optionally resolvins) can prevent DR, have cytoprotective actions and enhance the production of BDNF that has neuroprotective actions.

Our product SURYA-101 is a mixture of stabilized LXA4/NPD1/resolvins in a specific ratio that produces optimal anti-angiogenic, cytoprotective and maximal enhancement of the production of BDNF that serves as a potent anti-DR drug.