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AMELIORATION OF STZ-INDUCED DIABETIC CYSTOPATHY CAUSED BY N-HEXCOSANOL

Hypothesis / aims of study

Urinary tract dysfunctions are common clinical manifestations of diabetes mellitus, which are mainly induced by diabetic-associated neuropathy. In this study, we investigated the preventive effect of long-chain fatty alcohol (n-hexacosanol), a neurotrophic substance, on early phase of diabetes-induced bladder dysfunction in the rat.

Study design, materials and methods

Diabetes was induced in 8-week-old male Sprague-Dawley rats by administering an intraperitoneal injection of streptozotocin (50 mg/kg). The rats were divided randomly into four groups and maintained for four weeks: age-matched control rats, diabetic rats without treatment with n-hexacosanol, and diabetic rats treated with n-hexacosanol (2 and 8 mg/kg, i.p. every day). The serum glucose and serum insulin levels were determined, and the bladder functions were estimated by voiding behavior and cystometric studies, and fuctional studies to carbachol and KCl. Furthermore, we measured tissue levels of malonaldehyde (MDA), and examined possible diabetic induced histological changes in the rats.

Results

Treatment with n-hexacosanol did not alter diabetic status including body weight, bladder weight, serum glucose and serum insulin levels, but significantly improved the maximum contraction pressure of the detrusor and residual urine volume in cystometric studies and Emax values to carbachol in functional studies in a dose-dependent manner. The MDA concentration in the diabetic bladder was not altered by treatment with n-hexacosanol. Diabetes induced bladder smooth muscle hypertrophy, which was ameliorated by treatment with n-hexacosanol in a dose-dependent manner. Minute data are shown in the Tables.
A: control rats, B: diabetic rats, C: diabetic rats treated with FA (2 mg/kg), and D: diabetic rats treated with FA (8 mg/kg). Data are shown as mean ± SEM of six to eight separated determinations in each group. $P < 0.05$.

Table 1. General features of the experimental rats

	Body Weight (g)				
	8 weeks old	12 weeks old	Bladder weight (g)	Serum glucose (mg/dl)	Serum insulin (micro g/l)
A	267.1 ± 3.5	394.3 ± 3.7	0.104 ± 0.006	121.6 ± 10.1	2.56 ± 0.26
B	282.9 ± 8.8	260.0 ± 30.4 *	0.194 ± 0.021 *	356.9 ± 52.1 *	0.23 ± 0.15 *
C	261.5 ± 4.3	260.3 ± 23.7 *	0.195 ± 0.012 *	328.0 ± 16.2 *	0.19 ± 0.11 *
D	284.0 ± 9.4	305.3 ± 30.5 *	0.216 ± 0.022 *	335.4 ± 28.9 *	0.41 ± 0.19 *

*) significantly different from A group.

Table 2. Voiding behavior studies and cystometgram data in the experimental rats

	micturion frequency (/day)	urine production (ml/day)	Pdet (cmH_2O)	single voided volume (ml)	residual urine (ml)
A	11.7 ± 0.4	11.9 ± 3.8	37.6 ± 3.7	0.39 ± 0.05	0.005 ± 0.002
B	69.0 ± 3.3 *	143.3 ± 11.5 *	47.0 ± 2.0 *	0.70 ± 0.08 *	0.464 ± 0.054 **
C	66.7 ± 2.9 *	135.4 ± 6.9 *	42.8 ± 2.6	0.69 ± 0.11 *	0.218 ± 0.078 **
D	74.8 ± 3.5 *	153.0 ± 19.6 *	41.6 ± 5.9	0.68 ± 0.11 *	0.024 ± 0.016 ***

Pdet means maximum contraction pressure of the detrusor. Emax and ED50 values are for carbachol. *) significantly different from A group. **) significantly different from the other group. ***) significantly different from B and C groups.

Table 3. Functional studies and MDA measurement in the experimental rats

	Emax (g/mm^2)	ED_{50} (10^{-7} M)	KCl (g/mm^2)	MDA concetraltion (mM / gram tissue)
A	1.82 ± 0.16	14.4 ± 1.5	1.46 ± 0.18	9.4 ± 1.1
B	3.15 ± 0.24*	11.2 ± 1.3	1.65 ± 0.11	32.4 ± 3.0***
C	3.12 ± 0.52*	18.0 ± 6.4	1.53 ± 0.20	27.1 ± 1.6***
D	2.13 ± 0.21**	14.6 ± 2.1	1.24 ± 0.16	26.3 ± 3.4***

*) significantly different from A and D groups. **) significantly different from B and C groups. ***) significantly different from A group.

Interpretation of results

Although reatment with n-hexacosanol did not prevent an increase in the bladder weight and in micturition frequency, it should be noted that not only diabetes-associated neuropathy, but also diuresis induces hypertrophy in the rat detrusor [1]. Our data of voiding behavior and cystometric studies may be explained that diabetes induced diuresis masked the ameliorated effect of n-hexacosanol on the diabetic-induced cystopathy. However, treatment with n-hexacosanol markedly reduced the residual urine and E_{max} values for carbachol in a dose-dependent manner. Taken together, n-hexacosanol has a possibility to ameliorate diabetic-induced bladder dysfunction. Recently, Torimoto and his associates have reported that diabetes induces urethral dysfunction of relaxation during urination, which leads to increase in Pdet under urethane anesthesia [2]. Our data in cystometric studies were in agreement with their data. In addition, n-hexacosanol has a possibility to ameliorate diabetic induced urethral dysfunction. Damge et al (1995) reported that n-hexacosanol exert an inhibitory effect on insulin secretion stimulated by glucose in vivo and in vitro in the rat, suggesting a direct effect on islets of Langerhans [3]. Therefore, the finding that this drug does not influence serum glucose levels indicates that the mechanisms of its preventive effect on the diabetic rat bladder does not occur by reducing the serum glucose. These results, when taken together, suggest that n-hexacosanol directly modulates diabetes-damaged neurons while exerting weak scavenger effects. As the preventive effects of n-hexacosanol take place according to a mechanism that differs from that of insulin, it is possible that insulin treatment, if administered concomitant with n-hexacosanol treatment, may prevent diabetic peripheral neuropathy.

Concluding message

Although treatment with n-hexacosanol did not alter diabetic, diabetes induced-voiding dysfunction was ameliorated by treatment with n-hexacosanol in a dose-dependent manner. Our data indicated that n-hexacosanol could be an effective treatment against diabetes-induced bladder dysfunction.

References

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