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Chapter 1 : Neuropathy in experimental diabetes: an animal model. - Europe PMC Article - Europe PMC

2. Animal Models in Diabetic Neuropathy. Peripheral diabetic neuropathy (PDN) is a shattering complication of diabetes and leading cause of foot exclusion [].Clinical indications of PDN include increased vibration and thermal perception thresholds that progress to sensory loss, occurring in conjunction with degeneration of all fiber types in the peripheral nerve [].

This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract Diabetic or peripheral diabetic neuropathy PDN is one of the major complications among some other diabetic complications such as diabetic nephropathy, diabetic retinopathy, and diabetic cardiomyopathy. The use of animal models in the research of diabetes and diabetic complications is very common when rats and mice are most commonly used for many reasons. An animal model of diabetic or PDN should mimic the all major pathogeneses of human diabetic neuropathy. Hence, this review comparatively evaluates the animal models of diabetic and PDN which are developed since s with their advantages and disadvantages to help diabetic research groups in order to more accurately choose an appropriate model to meet their specific research objectives. In , Dobson Britain for the first time confirmed the presence of excess sugar in urine and blood as a cause of their sweetness. Depending on the pathogenesis, diabetes is classified as type 1 and type 2. The first widely accepted classification of diabetes mellitus was published by World Health Organization WHO in [2] and, in modified form, in [3]. The classification was widely accepted and used internationally even today. Since last few decades, diagnosis of diabetes is not only limited in blood and urine sugar levels but also in many other parameters and factors such as serum insulin levels, blood glycated haemoglobin and proteins, glucose tolerance ability, insulin sensitivity or insulin resistance, pancreatic beta-cell function, and so forth. Apart from above-mentioned parameters related abnormalities, diabetes patients are often suffered from other diabetes related complications such asâ€”diabetic neuropathy, diabetic cardiomyopathy, diabetic nephropathy DN , and diabetic retinopathy. These are usually caused by the poor glycemic control or improper management of diabetes mellitus. Amongst others, diabetic neuropathy is one the leading and painful complications usually suffered by many diabetic patients; however, the pathogenesis of this complication is still not fully understood due to the absence of an authentic animal model which fully mimics the complications of human diabetic neuropathy. Animal models in diabetes research are very common when most of the existing models are developed as a conventional model either for Type 1 or for T2D. But very often a conventional model of diabetes cannot demonstrate the specific pathogenesis of diabetes related complications. Therefore, the necessity of the individual and specific model for diabetic complications has been raised in the recent years to achieve the authentic outcomes of specific research aims. A number of animal models of diabetic neuropathy have been developed in last few decades approaching from diverse point of views. However, most of them did not receive much popularity because of their considerable number of limitations and disadvantages. In a comprehensive review, Harati [4] reported that the major handicap in studying diabetic neuropathies is the lack of a suitable animal model that addresses acute and chronic events leading to diabetic neuropathy. Hence, in this review, the pathogenesis, advantages, disadvantages, and limitations of several genetic and nongenetic animal models of diabetic neuropathy have been discussed to substantiate their efficacy for human study and in order to guide diabetes research groups to more accurately select the most appropriate models to address their specific research questions. Animal Models in Diabetic Neuropathy Peripheral diabetic neuropathy PDN is a shattering complication of diabetes and leading cause of foot exclusion [5]. Clinical indications of PDN include increased vibration and thermal perception thresholds that progress to sensory loss, occurring in conjunction with degeneration of all fiber types in the peripheral nerve [6]. A proportion of patients with PDN also describe abnormal sensations such as paresthesia, allodynia, hyperalgesia, and spontaneous pain that sometimes coexist with loss of normal sensory function [7

]. According to a recent review, a number of studies have investigated and described DN in mice, but it is difficult to compare these studies with each other or with human DN due to experimental differences including the animal strain, type of diabetes, method of induction, duration of diabetes, animal age, and gender [8]. Although two review articles [9 , 10] on animal models of diabetic and some other neuropathies are published recently, none of them suggested the most suitable model in order to study the further pathogenesis of diabetic neuropathy and also for the pharmacological screening and development of antidiabetic or anti-neuropathic drug in their reviews. This review precisely discussed the progress with the animal models of diabetic neuropathy which have been developed in last few decades since early s with their advantages, disadvantages, and limitations in order to assist scientists to more appropriately choose a model based on their specific research aims. Additionally, the characterization of neuropathy or advantages and limitations or disadvantages of most of the models are summarized in Table 1. Characterization criteria advantages and limitations disadvantages of some selective animal models of diabetic neuropathy developed since s. Models Developed during s and s The nerve conduction and regenerative changes in experimental diabetes were first noticed by Eliasson during [11 , 12]; however, the first peripheral neuropathy in alloxan-diabetic rats was reported by Preston in [13] then Lovelace in [14]. After that a number of scientists reported diabetic neurophaty mostly in alloxan-induced diabetic models. A complete animal rat model of diabetic neuropathy DN was first reported by Jakobsen and Lundbeck in [15] with reduced sizes of nerve fiber, axon, and myelin sheath, which contribute in impaired motor function in streptozotocin STZ -induced diabetic rats. The PDN was initially characterized by severely decreased motor nerve conduction velocity MNCV , absence of large myelinated fibers, and axonal atrophy in this mouse model. In the further evaluation studies, axonal changes as well as axonal dystrophy were observed in the myelinated and unmyelinated fibers followed by loss, shrinkage, and breakdown of myelin sheath in the later stage. However, the major limitation is that none of these models have been evaluated by using anti-diabetic or antineuropathic drugs. However, there was no reduction in nerve fiber diameters or other signs of abnormal morphology that could be correlated with these physiological effects. Hence, further study is warranted to use this animal as a model for human PDN. They found significantly reduced motor nerve conduction velocities and prolonged F-wave latencies in diabetic animals compared to nondiabetic control animals, while motor-evoked amplitudes did not differ. Additionally, nerve conduction times were increased in motor fibers of diabetic animals two years after the onset of diabetic hyperglycemia. Although these abnormalities are similar to those seen in humans, further study is needed to establish this primate model for human PDN since these models have not been evaluated by any antineuropathic drugs. Additionally, after comparing with diabetic and hypoglycaemic neuropathy, Sima et al. So this particular factor needs to be considered before choosing any animal model for a diabetic neuropathic study. Models Developed during s 2. This model was characterized by slower motor nerve conduction and temporal dispersion of compound muscle action potential. Structural de- and remyelinations were observed in the sciatic and tibial nerves in month-old rats, while month-old rats additionally showed axonal degeneration and dystrophy, reduced myelinated fiber occupancy, and decreased mean myelinated fiber size. Additionally, these neuropathic manifestations are unique as compared with those found in other spontaneously diabetic animal models. Twenty percent L-fucose diet resulted in significant axonal atrophy, paranodal swelling, and paranodal demyelination without increasing Walleran degeneration or nerve fiber loss. After this study, it has been recommended that this L-fucose model can serve as an experimental tool to study the diabetic neuropathy. STZ-induced diabetic animals were chronically ill, with reduced growth rate, polyuria, diarrhoea, and enlarged and distended bladders when these symptoms were not found in sciatic nerve ligated model. This sciatic nerve ligated model has also been evaluated with antineuropathic drugs Morphine and L-Baclofen , which produce greater reversal of mechanical hyperalgesia following partial nerve ligation. They also added that STZ-induced diabetes in rats produces long-lasting mechanical but not thermal hyperalgesia. Although evaluated by antineuropathic drugs, further study is needed to understand the induction of the major pathogenesis of PDN. It was found that after only 3â€”5 weeks of diabetes, NOD mice developed markedly

swollen axons and dendrites neurotic dystrophy in the prevertebral superior mesenteric and celiac ganglia SMG-CG , similar to the pathology described in diabetic STZ- and BBW-rat and human. STZ-induced diabetic mice develop identical changes, although at a much slower pace and to a lesser degree than NOD mice. Therefore, NOD mouse appears to be a valuable model of diabetic sympathetic autonomic neuropathy which is consistent with the pathogenesis of other rodent models and human. It has been further supported by a very recently published comparative study on peripheral neuropathy between NOD and ICR diabetic mice [30] where NOD mice have been suggested as a better model than ICR mice particularly in terms of nerve regeneration. Genetic Rodent Models The development of peripheral diabetic neuropathy has been assessed by longitudinal memory performance in spontaneously induced Type 1 diabetic Ins2C96Y Akita mice by Choeiri et al. This model was characterized by reduced number of beta cells with hypoinsulinemia, progressive hyperglycemia, and reduced sensory nerve conduction velocity; however no significant deficit has been detected as Morris water maze trial compared to the control group, and many other diabetic neuropathy-related major parameters have not been measured. Later, after measuring a number of diabetic neuropathy related parameters, Schmidt et al. This model has been evaluated by progressively developed markedly swollen axons and dendrites which are the common signs of neurotic dystrophy. According to the above-mentioned studies, although Ins2 Akita mice can be a proper genetic model of diabetic neuropathy, this model needs to be evaluated by antidiabetic and antineuropathic drugs. This animal model was also successfully evaluated by a potent inhibitor of PDN such as aldose reductase inhibitor which normalized motor and sensory nerve conduction velocity. On the other hand, Kamenov et al. In this regard, each type of animal has been divided into 2 subgroups and fed with or without sucrose-containing diets for 2 months and found that the blood glucose and HbA1c levels were significantly higher in OLETF rats, when compared with those in control LETO rats. Motor nerve conduction velocity and thermal nociception were significantly decreased in OLETF rats in their 10 months of age, while the values of the tail pressure test did not differ compared with those from LETO rats. Additionally, in order to induce nerve damage, after 4 weeks of sustained hyperglycemia, the left sciatic nerve was exposed by blunt dissection and crushed at the femur major trochanter level for three times in succession for 30 seconds in anaesthetized animals when intact contralateral nerve was used as a control. This transgenic model was evaluated by significant hyperglycemia, slower tibial sensory nerve conduction velocity SNCV and increased motor latencies and duration of compound muscle potential, reduced nerve fiber density, and so on. The slower recovery of nerve conduction velocities were observed in the diabetic transgenic mice group compared to the control. Although this model has been displayed most of the major pathogenesis of peripheral diabetic neuropathy, a sophisticated surgical approach has been used with multiple STZ injections to develop this model, and it has not been evaluated by any antidiabetic or antineuropathic drugs. Experimentally-Induced Models Filho and Fazan [22] developed a streptozotocin STZ -induced model of phrenic nerve neuropathy in rats. Diabetes was induced by a single injection of streptozotocin to penile vein, and higher blood glucose level confirmed the diabetic state. Left and right fascicular areas and diameter of the phrenic nerves were significantly decreased in the proximal segments and right segments, respectively. The phrenic nerves of diabetic rats showed smaller myelinated axon diameters compared to controls. The g ratio for diabetic rats was significantly lower than the controls when these changes have been restored by the daily injection s. Although this model has been evaluated by insulin, no antineuropathic drug has been used for the evaluation of this model. This model was characterized by the deficit of motor and sensory nerve conductions, tactile allodynia, and thermal hypoalgesia; however intradermal nerve fiber loss or axonal atrophy was absent in this model. Although plasma FFA and insulin concentrations were increased and glucose tolerance was impaired, the frank hyperglycemia was absent in this model. According to the data, although this model can be used for prediabetes and obesity related neuropathy, it cannot be used for chronic diabetic neuropathy. This model has also not been evaluated by any antineuropathic drug, and the duration of model development time is one of the major concerns. In , Hong and Kang [40] published a very special finding on auditory neuropathy in streptozotocin-induced diabetic ICR mice in order to understand the

possible auditory damage. From the data of this study, authors suggested that the STZ-induced mouse can be used for the evaluation of auditory pathway impairment via ABR and AMLR tests, however this model has not been evaluated by any antidiabetic or antineuropathic drugs. At the same year, Vareniuk et al. Although the STZ injected model was not evaluated by any antidiabetic or antineuropathic drugs, but from this study it is clear that iNOS gene plays a major role in the induction or peripheral diabetic neuropathy which can be future research and drug development target. Recently, Muthuraman and colleagues [36] developed a rat model of vasculatic neuropathy by ischemic perfusion in the rat femoral artery. This model was validated after 2, 4, and 6 h of ischemia followed by prolonged reperfusion. The model has been characterized by thermal and mechanical hyperalgesia in paw and tail which are associated with peripheral and central neuropathic pain, respectively. The serum IL, nerve fiber density, and nerve conduction velocity were lower, and serum nitrate, malondialdehyde MDA and TNF-alpha levels were higher in this model. Although neuropathy induction period of this model is very short and has similar pathogenesis with human diabetic neuropathy, the pathogenesis of neuropathy have not been developed here via hyperglycaemia, what is usually happened in diabetic neuropathy, but via ischemic perfusion in the animal femoral artery. Hence, this model cannot be a better model to study human peripheral diabetic neuropathy. Additionally, this model has not been evaluated by using any antineuropathic drugs. Apart from common diabetic abnormalities such as sustained hyperglycemia and dyslipidemia, this diabetic peripheral neuropathic model was further characterized by significantly delayed and lower motor nerve conduction velocity from 24 weeks and significantly lower number of sural nerve fibers at the end of the week experimental period. Additionally, thickened epineurial arterioles were frequently found in this model. So this model can be a better diabetic peripheral neuropathic model not only to understand the pathogenesis of diabetic peripheral neuropathy but also to screen and develop antidiabetic peripheral neuropathic drug, particularly for Type 2 diabetes. It was also characterized by increased body weight, hyperlipidemia, hyperglycemia, and the evidence of neuropathy; however this model was not delivered by lipid profile usually seen in translational diabetic neuropathy. Although this model has been characterized by significantly lower tail flick response to heat stimulus, sciatic motor nerve conduction velocity, and intraepididymal nerve fiber velocity, mismatched results were observed for the body weight, blood glucose, plasma lipids, and total blood glycated haemoglobin. From the results of this study, authors suggested that the overall effects of ApoE knockout, either directly upon nerve structure and function or indirectly on lipid metabolism, are insufficient to significantly alter the course of translational diabetic neuropathy research, and further therapeutic intervention is necessary in this regard. Apart from the above limitations, this model was also not evaluated by any antidiabetic or antineuropathic drug. Diabetes was developed by a single injection i. This model has been evaluated by significantly lower sensory nerve conduction velocity SNCV , higher nociceptive threshold, hypoalgesia, and reduced axon area of unmyelinated nerve fibers or unmyelinated fiber atrophy. Although no difference was found for the myelinated nerve fiber areas between the diabetic and healthy mice, this model has been successfully evaluated by insulin treatment.

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Chapter 2 : Animal Models of Diabetes and Metabolic Disease - Europe PMC Article - Europe PMC

Diabetic neuropathy (DN) is a multifactor complication of diabetes. It is a late finding in type 1 diabetes, but can be an early finding in type 2 diabetes. The cause of DN is still unclear and, like other complications of diabetes, it may be the result of various pathological conditions. Animal.

Find articles by A. Somani Find articles by R. This article has been cited by other articles in PMC. Abstract Diabetic neuropathy DN is a multifactor complication of diabetes. It is a late finding in type 1 diabetes, but can be an early finding in type 2 diabetes. The cause of DN is still unclear and, like other complications of diabetes, it may be the result of various pathological conditions. Animal models and biomarkers of DN have been extensively used in neuropathic research. The most useful model of DN should exhibit the key feature present in human pathology. Diabetic rodents show behavioral, functional, structural and molecular biomarkers and they are widely used as models to investigate the etiology of DN as well as to screen the efficacy of the potential therapeutic interventions. We have reviewed the different animal models and biomarkers of neuropathy in diabetic rodents of either type 1 or type 2 diabetes. Biomarker, diabetic neuropathy, diabetic rodents Neuropathy is the most common complication of diabetes mellitus DM. The selected animal model of DN should exhibit the features present in human pathology. Diabetic rodents show many abnormalities that are seen in diabetic patients with neuropathy, including hyperalgesia, allodynia, slow nerve conduction velocity NCV and progressive sensory and sensory motor deficit. The decision to select the animal model for a particular protocol is very important. There are advantages and disadvantages to each model for the investigation of rodent DN. It is important to know about the different biomarkers of neuropathy in diabetic rodents and the time it takes to develop after the induction of diabetes. The aim of this review is to highlight the available animal models and biomarkers of DN in rodents. This will provide adequate tools to investigate the mechanism of action of drugs with potential activity in DN as well as the etiological factors in the pathogenesis of DN. In Vivo Animal Models of DN There are various models available, including models of type 1 and type 2 diabetes, for the study of neuropathy in rodents. Animal models that are used to study DN are broadly divided into two classes: Induced models are further subdivided as drug-induced and diet-induced models of DN [Table 1]. The HFD-fed mouse is a model for studying the pathogenesis of neuropathic changes developing in human subjects with IGT, obesity and metabolic syndrome. In human type 2 diabetes, neuropathy often precedes the diagnosis of diabetes, making it difficult to stage these patients. It is hoped that animal studies of type 2 diabetes can lead to more meaningful details of the progression of nerve dysfunction in these patients. Various neuropathic changes manifested in genetic models of diabetes are mentioned in Table 2. Table 2 Neuropathic changes occurring in the genetic models of diabetes[3] Animal models.

Chapter 3 : Animal Models of Diabetes and Metabolic Disease

Diabetic or peripheral diabetic neuropathy (PDN) is one of the major complications among some other diabetic complications such as diabetic nephropathy, diabetic retinopathy, and diabetic cardiomyopathy. The use of animal models in the research of diabetes and diabetic complications is very common.

Not validated by antineuropathic drug. Spontaneously induced Ins2 Akita mouse model Choeiri et al. Not validated by anti-diabetic or antineuropathic drug. May not be widely available for routine pharmacological screening of anti-diabetic or anti-neuropathic drugs. Surgically-induced neuropathic model i Thermal and mechanical hyperalgesia in paw and tail. Genetically modified SDT fatty rat model Yamaguchi et al. Some pathogenesis was induced only after a long period of time such as 40 weeks. Open in a separate window 2. Models Developed during s and s The nerve conduction and regenerative changes in experimental diabetes were first noticed by Eliasson during [11 , 12]; however, the first peripheral neuropathy in alloxan-diabetic rats was reported by Preston in [13] then Lovelace in [14]. After that a number of scientists reported diabetic neurophaty mostly in alloxan-induced diabetic models. A complete animal rat model of diabetic neuropathy DN was first reported by Jakobsen and Lundbeck in [15] with reduced sizes of nerve fiber, axon, and myelin sheath, which contribute in impaired motor function in streptozotocin STZ -induced diabetic rats. The PDN was initially characterized by severely decreased motor nerve conduction velocity MNCV , absence of large myelinated fibers, and axonal atrophy in this mouse model. In the further evaluation studies, axonal changes as well as axonal dystrophy were observed in the myelinated and unmyelinated fibers followed by loss, shrinkage, and breakdown of myelin sheath in the later stage. However, the major limitation is that none of these models have been evaluated by using anti-diabetic or antineuropathic drugs. However, there was no reduction in nerve fiber diameters or other signs of abnormal morphology that could be correlated with these physiological effects. Hence, further study is warranted to use this animal as a model for human PDN. They found significantly reduced motor nerve conduction velocities and prolonged F-wave latencies in diabetic animals compared to nondiabetic control animals, while motor-evoked amplitudes did not differ. Additionally, nerve conduction times were increased in motor fibers of diabetic animals two years after the onset of diabetic hyperglycemia. Although these abnormalities are similar to those seen in humans, further study is needed to establish this primate model for human PDN since these models have not been evaluated by any antineuropathic drugs. Additionally, after comparing with diabetic and hypoglycaemic neuropathy, Sima et al. So this particular factor needs to be considered before choosing any animal model for a diabetic neuropathic study. Models Developed during s 2. This model was characterized by slower motor nerve conduction and temporal dispersion of compound muscle action potential. Structural de- and remyelinations were observed in the sciatic and tibial nerves in month-old rats, while month-old rats additionally showed axonal degeneration and dystrophy, reduced myelinated fiber occupancy, and decreased mean myelinated fiber size. Additionally, these neuropathic manifestations are unique as compared with those found in other spontaneously diabetic animal models. Twenty percent L-fucose diet resulted in significant axonal atrophy, paranodal swelling, and paranodal demyelination without increasing Walleran degeneration or nerve fiber loss. After this study, it has been recommended that this L-fucose model can serve as an experimental tool to study the diabetic neuropathy. STZ-induced diabetic animals were chronically ill, with reduced growth rate, polyuria, diarrhoea, and enlarged and distended bladders when these symptoms were not found in sciatic nerve ligated model. This sciatic nerve ligated model has also been evaluated with antineuropathic drugs Morphine and L-Baclofen , which produce greater reversal of mechanical hyperalgesia following partial nerve ligation. They also added that STZ-induced diabetes in rats produces long-lasting mechanical but not thermal hyperalgesia. Although evaluated by antineuropathic drugs, further study is needed to understand the induction of the major pathogenesis of PDN. It was found that after only 3â€”5 weeks of diabetes, NOD mice developed markedly swollen axons and dendrites neurotic dystrophy in the prevertebral superior mesenteric and celiac ganglia

SMG-CG , similar to the pathology described in diabetic STZ- and BBW-rat and human. STZ-induced diabetic mice develop identical changes, although at a much slower pace and to a lesser degree than NOD mice. Therefore, NOD mouse appears to be a valuable model of diabetic sympathetic autonomic neuropathy which is consistent with the pathogenesis of other rodent models and human. It has been further supported by a very recently published comparative study on peripheral neuropathy between NOD and ICR diabetic mice [30] where NOD mice have been suggested as a better model than ICR mice particularly in terms of nerve regeneration. Genetic Rodent Models The development of peripheral diabetic neuropathy has been assessed by longitudinal memory performance in spontaneously induced Type 1 diabetic Ins2C96Y Akita mice by Choeiri et al. This model was characterized by reduced number of beta cells with hypoinsulinemia, progressive hyperglycemia, and reduced sensory nerve conduction velocity; however no significant deficit has been detected as Morris water maze trial compared to the control group, and many other diabetic neuropathy-related major parameters have not been measured. Later, after measuring a number of diabetic neuropathy related parameters, Schmidt et al. This model has been evaluated by progressively developed markedly swollen axons and dendrites which are the common signs of neurotic dystrophy. According to the above-mentioned studies, although Ins2 Akita mice can be a proper genetic model of diabetic neuropathy, this model needs to be evaluated by antidiabetic and antineuropathic drugs. This animal model was also successfully evaluated by a potent inhibitor of PDN such as aldose reductase inhibitor which normalized motor and sensory nerve conduction velocity. On the other hand, Kamenov et al. In this regard, each type of animal has been divided into 2 subgroups and fed with or without sucrose-containing diets for 2 months and found that the blood glucose and HbA1c levels were significantly higher in OLETF rats, when compared with those in control LETO rats. Motor nerve conduction velocity and thermal nociception were significantly decreased in OLETF rats in their 10 months of age, while the values of the tail pressure test did not differ compared with those from LETO rats. Additionally, in order to induce nerve damage, after 4 weeks of sustained hyperglycemia, the left sciatic nerve was exposed by blunt dissection and crushed at the femur major trochanter level for three times in succession for 30 seconds in anaesthetized animals when intact contralateral nerve was used as a control. This transgenic model was evaluated by significant hyperglycemia, slower tibial sensory nerve conduction velocity SNCV and increased motor latencies and duration of compound muscle potential, reduced nerve fiber density, and so on. The slower recovery of nerve conduction velocities were observed in the diabetic transgenic mice group compared to the control. Although this model has been displayed most of the major pathogenesis of peripheral diabetic neuropathy, a sophisticated surgical approach has been used with multiple STZ injections to develop this model, and it has not been evaluated by any antidiabetic or antineuropathic drugs. Experimentally-Induced Models Filho and Fazan [22] developed a streptozotocin STZ -induced model of phrenic nerve neuropathy in rats. Diabetes was induced by a single injection of streptozotocin to penile vein, and higher blood glucose level confirmed the diabetic state. Left and right fascicular areas and diameter of the phrenic nerves were significantly decreased in the proximal segments and right segments, respectively. The phrenic nerves of diabetic rats showed smaller myelinated axon diameters compared to controls. The g ratio for diabetic rats was significantly lower than the controls when these changes have been restored by the daily injection s. Although this model has been evaluated by insulin, no antineuropathic drug has been used for the evaluation of this model. This model was characterized by the deficit of motor and sensory nerve conductions, tactile allodynia, and thermal hypoalgesia; however intradermal nerve fiber loss or axonal atrophy was absent in this model. Although plasma FFA and insulin concentrations were increased and glucose tolerance was impaired, the frank hyperglycemia was absent in this model. According to the data, although this model can be used for prediabetes and obesity related neuropathy, it cannot be used for chronic diabetic neuropathy. This model has also not been evaluated by any antineuropathic drug, and the duration of model development time is one of the major concerns. In , Hong and Kang [40] published a very special finding on auditory neuropathy in streptozotocin-induced diabetic ICR mice in order to understand the possible auditory damage. From the data of this study, authors suggested that the STZ-induced mouse can be

used for the evaluation of auditory pathway impairment via ABR and AMLR tests, however this model has not been evaluated by any antidiabetic or antineuropathic drugs. At the same year, Vareniuk et al. Although the STZ injected model was not evaluated by any antidiabetic or antineuropathic drugs, but from this study it is clear that iNOS gene plays a major role in the induction or peripheral diabetic neuropathy which can be future research and drug development target. Recently, Muthuraman and colleagues [36] developed a rat model of vasculatic neuropathy by ischemic perfusion in the rat femoral artery. This model was validated after 2, 4, and 6 h of ischemia followed by prolonged reperfusion. The model has been characterized by thermal and mechanical hyperalgesia in paw and tail which are associated with peripheral and central neuropathic pain, respectively. The serum IL, nerve fiber density, and nerve conduction velocity were lower, and serum nitrate, malondialdehyde MDA and TNF-alpha levels were higher in this model. Although neuropathy induction period of this model is very short and has similar pathogenesis with human diabetic neuropathy, the pathogenesis of neuropathy have not been developed here via hyperglycaemia, what is usually happened in diabetic neuropathy, but via ischemic perfusion in the animal femoral artery. Hence, this model cannot be a better model to study human peripheral diabetic neuropathy. Additionally, this model has not been evaluated by using any antineuropathic drugs. Apart from common diabetic abnormalities such as sustained hyperglycemia and dyslipidemia, this diabetic peripheral neuropathic model was further characterized by significantly delayed and lower motor nerve conduction velocity from 24 weeks and significantly lower number of sural nerve fibers at the end of the week experimental period. Additionally, thickened epineurial arterioles were frequently found in this model. So this model can be a better diabetic peripheral neuropathic model not only to understand the pathogenesis of diabetic peripheral neuropathy but also to screen and develop antidiabetic peripheral neuropathic drug, particularly for Type 2 diabetes. It was also characterized by increased body weight, hyperlipidemia, hyperglycemia, and the evidence of neuropathy; however this model was not delivered by lipid profile usually seen in translational diabetic neuropathy. Although this model has been characterized by significantly lower tail flick response to heat stimulus, sciatic motor nerve conduction velocity, and intraepididymal nerve fiber velocity, mismatched results were observed for the body weight, blood glucose, plasma lipids, and total blood glycated haemoglobin. From the results of this study, authors suggested that the overall effects of ApoE knockout, either directly upon nerve structure and function or indirectly on lipid metabolism, are insufficient to significantly alter the course of translational diabetic neuropathy research, and further therapeutic intervention is necessary in this regard. Apart from the above limitations, this model was also not evaluated by any antidiabetic or antineuropathic drug. Diabetes was developed by a single injection i. This model has been evaluated by significantly lower sensory nerve conduction velocity SNCV , higher nociceptive threshold, hypoalgesia, and reduced axon area of unmyelinated nerve fibers or unmyelinated fiber atrophy. Although no difference was found for the myelinated nerve fiber areas between the diabetic and healthy mice, this model has been successfully evaluated by insulin treatment. Since the unmyelinated nerve fibers were more affected than myelinated nerve fibers and it has been successfully evaluated with insulin treatment, so it can be a better model to study the human sensory polyneuropathy. Conclusion As per this review, although a number of approaches have been used to develop the diabetic neuropathic models in different strains of animals in last five decades, none of them are without limitations. Some models such as streptozotocin-induced rats, Chinese hamster, rhesus monkey, partial sciatic nerve ligated rats, and Otsuka Long-Evans Tokushima Fatty OLETF rats developed very few major or some minor pathogenesis of diabetic neuropathy and peripheral diabetic neuropathy and the model development time for some of these models were very long. The best model of diabetic neuropathy or peripheral diabetic neuropathy should have some major criteria such as: Although L-fucose induced neuropathic rats, OLETF rats, and genetically modified SDT rats have shown some promising pathogenesis of diabetic and PDN, further studies are needed to understand the suitability and usefulness of these models for diabetic or peripheral diabetic neuropathic researches.

Chapter 4 : Animal models and biomarkers of neuropathy in diabetic rodents

Diabetic neuropathy is not a single but several different pathogenic mechanisms leading to several symptoms. Diabetic animal models have been extensively used to characterize these mechanisms to evaluate potential treatments in humans.

Received Apr 3; Accepted Apr 3. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. This article has been cited by other articles in PMC. Metabolic diseases, including diabetes and its complications , obesity, dyslipidemia, and hypertension, are common diseases and frequently occur in combination. Although molecular biological techniques have become more important for clarifying the mechanisms of the diseases, the importance of animal models has not changed. Animal models are needed to reveal the underlying pathophysiology of metabolic diseases; this approach provides information that is the key to the development of new therapies and drugs to treat and manage these diseases. In this special issue, we aim to provide information on recent beneficial experimental animal models in this field and present up-to-date information on the pathophysiology, therapeutic drugs, and diagnosis of metabolic diseases using valuable animal models. We believe that the 14 articles in this special issue satisfy these aims. Type 2 diabetes T2D is a complex, multifactorial disease. Both genetic and environmental factors are known to contribute to its development; however, the precise pathogenesis of T2D remains largely unclear. Several new animal models are introduced in this special issue. Among these diabetic complications, ocular complications are notably a unique characteristic of this animal model. Using this model, A. This new T2D model is derived from the ZF rat, presents with hyperglycemia, and is phenotypically distinct from normoglycemic ZF rats. Loss of islet architecture and fibrosis are also observed in the ZFDM rat. This model is useful for investigating young- to middle-aged adult-onset T2D. This model is useful in investigations on the progression of T2D with age. Three articles describe genetic factors of spontaneous T2D models, in detail. Their new congenic strain, carrying a single QTL, may be helpful in identifying the causative gene and should aid future investigations on understanding the mechanism by which obesity interacts with QTLs to regulate diabetic traits. The consomic strains constructed in their studies will facilitate fine mapping and identification of responsible genes for T2D-related phenotypes. Islet transplantation is an effective treatment for severe diabetes. Cardiovascular disorders CVDs are the leading cause of death in humans. The use of different experimental models is important in order to better understand the mechanisms involved in CVDs caused by metabolic disease. Both environmental and genetic factors are known to contribute to the progression of this autoimmunity. In addition, this review discusses genetically manipulated NOD mice that overexpress protective genes in islet, T-cell receptors, islet-specific neoantigens, or humanized MHC. Pezzolesi Norihide Yokoi Norihide Yokoi.

Chapter 5 : Animal Models of Diabetic Neuropathy: Progress Since s

There are various models available, including models of type 1 and type 2 diabetes, for the study of neuropathy in rodents. Animal models that are used to study DN are broadly divided.

 Metabolic diseases, including diabetes and its complications , obesity, dyslipidemia, and hypertension, are common diseases and frequently occur in combination. Although molecular biological techniques have become more important for clarifying the mechanisms of the diseases, the importance of animal models has not changed. Animal models are needed to reveal the underlying pathophysiology of metabolic diseases; this approach provides information that is the key to the development of new therapies and drugs to treat and manage these diseases. In this special issue, we aim to provide information on recent beneficial experimental animal models in this field and present up-to-date information on the pathophysiology, therapeutic drugs, and diagnosis of metabolic diseases using valuable animal models. We believe that the 14 articles in this special issue satisfy these aims. Type 2 diabetes T2D is a complex, multifactorial disease. Both genetic and environmental factors are known to contribute to its development; however, the precise pathogenesis of T2D remains largely unclear. Several new animal models are introduced in this special issue. Among these diabetic complications, ocular complications are notably a unique characteristic of this animal model. Using this model, A. This new T2D model is derived from the ZF rat, presents with hyperglycemia, and is phenotypically distinct from normoglycemic ZF rats. Loss of islet architecture and fibrosis are also observed in the ZFDM rat. This model is useful for investigating young- to middle-aged adult-onset T2D. This model is useful in investigations on the progression of T2D with age. Three articles describe genetic factors of spontaneous T2D models, in detail. Their new congenic strain, carrying a single QTL, may be helpful in identifying the causative gene and should aid future investigations on understanding the mechanism by which obesity interacts with QTLs to regulate diabetic traits. However, hyperglycemia and STZ sensitivity in heterozygous mouse was not as severe as in the homozygous mouse. The consomic strains constructed in their studies will facilitate fine mapping and identification of responsible genes for T2D-related phenotypes. Islet transplantation is an effective treatment for severe diabetes. Cardiovascular disorders CVDs are the leading cause of death in humans. The use of different experimental models is important in order to better understand the mechanisms involved in CVDs caused by metabolic disease. Both environmental and genetic factors are known to contribute to the progression of this autoimmunity. In addition, this review discusses genetically manipulated NOD mice that overexpress protective genes in islet, T-cell receptors, islet-specific neoantigens, or humanized MHC.