subtype CMT2A, is caused by mutations in the *MFN2* gene coding for mitofusin 2, a dynamin-like GTPase located in the outer membrane of mitochondria. MFN2 is involved in several cellular processes such as the fusion of mitochondrial membranes, the transport of mitochondria along axons, and the tethering of mitochondria .with endoplasmic reticulum. To date, more than 70 mutations associated with CMT2A and complicated variants of CMT2 have been described. They are mainly point mutations with dominant transmission, but recently some semidominant and recessive mutations have been reported. The understanding of the mechanisms by which the mutated forms of MFN2 lead to neurodegeneration is limited by the fact that few mouse models for CMT2A were successfully developed. As zebrafish have become useful to study many neurological and neuromuscular disorders, we decided to use this model to investigate the function of *MFN2* and its role in CMT2A disease. Using the morpholino technique, we knocked down MFN2 in developing embryos, which resulted in severely motor-impaired fish in accordance with the loss of limbs motility observed in CMT2A patients. Investigations performed on the neuromuscular system of morphants demonstrated that larvae exhibit misshapen motor neurons and a reduction of the neuromuscular junction formation. As in human diseases, probably because of their incorrect innervation, muscular fibers appear hypotrophic and are reduced in diameter. Our results, validated by the rescue of morphants with human *MFN2* mRNA, confirm the essential role of MFN2 in motor neuron development and suggest that the zebrafish could be a very useful tool to study in living embryos the effects of mutations identified in CMT2A patients.

REGRESSION OF DIABETIC NEUROPATHY BY SUCCESSFUL ISLET TRANSPLANTATION IN LONG-TERM STZ-DIABETIC RATS

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Despite optimal glycemic control by intensive insulin administration that can significantly reduce but not abolish the incidence of diabetic complications, these complications are still the major cause of morbidity and mortality in diabetic patients. We have shown that the transplantation of microencapsulated syngenic islets in 2-month streptozotocin (STZ)-induced diabetic rats produces normoglycemia, a rise in body weight, amelioration of impaired nociceptive thresholds, and normalization of tail nerve conduction velocity (NCV) and of Na+,K+-ATPase in the sciatic nerve. No data are available on the long-term effect of pancreatic islet transplantation in long-lasting diabetes regarding the effect, in particular, on peripheral neuropathy. We investigated the effects of immunoisolated islet transplantation on diabetic neuropathy in 4-month diabetic rats in the same model. In addition, we compared the effects obtained by islet transplantation with those achieved with strict glycemic control by insulin administration. To this end, we investigated three groups of Sprague-Dawley rats: healthy control rats, untreated diabetic rats, and diabetic rats with 300–400 mg/dl of insulin-regulated glycemia. After 4 months, diabetic rats with 300–400 mg/dl of insulin-regulated glycemia were divided into three subgroups: the first maintained the same condition, the second were transplanted with microencapsulated islets (from Lewis rats) into the peritoneal cavity, and the last were insulin treated to adjust glycemia between 200 and 300 mg/dl; insulin treatments and transplantation lasted another 4 months so that the overall duration of the study was 8 months from diabetes induction. Our data show that microencapsulated allogenic islet transplantation in STZ-induced diabetic animals allows control of glycemia in a physiological way in 5 of 11 transplanted rats, accompanied by a rise in body and muscle weight. In these rats, transplantation significantly improved tail NCV and Na+,K+-ATPase, restored thermal and ameliorated mechanical nociceptive thresholds. The near good glycemia-adjusted rat group showed similar although less pronounced improvements. Poor glycemic control was seen in six islet transplanted "non-responder" rats, and the 300–400 mg/dl insulin-regulated glycemia group showed neuropathic changes similar to the untreated STZ-induced diabetic group. In conclusion, our results show that successful allogenic islet transplantation induces effective regression or retardation of the progression of established neuropathy associated with diabetes. Despite raising different questions to be solved by future research programs, these findings strongly indicate successful strategies related to a more physiological and safe glycemic control.

MECHANISMS OF PAIN IN DISTAL SYMMETRIC POLYNEUROPATHY. A COMBINED CLINICAL AND NEUROPHYSIOLOGICAL STUDY

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