Vigneron, D.B., and Goga, A. (2011). Cell Metab. *14*, 131–142.

Metallo, C.M., Gameiro, P.A., Bell, E.L., Mattaini, K.R., Yang, J., Hiller, K., Jewell, C.M., Johnson, Z.R., Irvine, D.J., Guarente, L., et al. (2011). Nature. Published online November 20, 2011. 10.1038/nature10602.

Tran, P.T., Fan, A.C., Bendapudi, P.K., Koh, S., Komatsubara, K., Chen, J., Horng, G., Bellovin, D.I., Giuriato, S., Wang, C.S., et al. (2008). PLoS ONE *3*, e2125. 10.1371/journal.pone.0002125.

Trusolino, L., Bertotti, A., and Comoglio, P.M. (2010). Nat. Rev. Mol. Cell Biol. *11*, 834–848.

Wise, D.R., and Thompson, C.B. (2010). Trends Biochem. Sci. *35*, 427–433.

Yuneva, M.O., Fan, T.W.M., Allen, T.D., Higashi, R.M., Ferraris, D.V., Tsukamoto, T., Mates, J.M., Alonso, F.J., Wang, C., Seo, Y., et al. (2012). Cell Met. *15*, this issue, 157–170.

Neuron Transplantation Partially Reverses an Obesity Disorder in Mice

Scott M. Sternson[1,*]
[1]Janelia Farm Research Campus, HHMI, Ashburn, VA 20147, USA
*Correspondence: sternsons@janelia.hhmi.org
DOI 10.1016/j.cmet.2012.01.011

Mice lacking leptin receptors are grossly obese and diabetic, in part due to dysfunction in brain circuits important for energy homeostasis. Transplantation of leptin receptor-expressing hypothalamic progenitor neurons into the brains of leptin receptor deficient mice led to integration into neural circuits, reduced obesity, and normalized circulating glucose levels.

Neuron transplantation has been explored as a treatment for debilitating conditions, including Parkinson's disease, blindness, and stroke. In *Science,* Czupryn et al. (2011) report the capacity of neural transplantation to reverse the consequences of a genetic defect in leptin signaling. This study shows that obesity and diabetes in mice lacking the leptin receptor can be partially reversed after transplanting hypothalamic cells from mice with functional leptin receptors.

The hormone leptin (Zhang et al., 1994) is produced by adipose tissue and broadcasts energetic status to the rest of the body. Previous work has demonstrated that leptin receptor expression in neurons is essential for preventing obesity (Cohen et al., 2001). Moreover, leptin receptor expression in specific classes of neurons rescues discrete aspects of energy homeostasis in leptin receptor null (*db*/*db*) mice (Kowalski et al., 2001). Czupryn et al. pursued a creative approach to examine the development and function of leptin-sensitive neural circuits. They used ultrasound-guided microtransplantation to graft leptin receptor expressing neurons into the hypothalamus of newborn *db*/*db* mice. The researchers asked three main questions: (1) Would transplanted neural progenitors differentiate into regionally appropriate neuron classes? (2) Would transplanted neurons incorporate into neural circuits with host neurons? (3) Would the metabolic phenotype associated with the *db* mutation be affected by transplantation of a small number of leptin receptor-expressing cells?

To address the first two questions, the researchers transplanted cells carrying a green fluorescent protein transgene, which allowed them to be identified for analysis and compared to surrounding host cells. Hypothalamic grafts differentiated into electrophysiologically and histochemically determined neuronal cell types that were consistent with previously characterized hypothalamic populations. Donor cells integrated into local circuits by receiving functional synaptic connections. Importantly, some of the transplanted cells were leptin responsive. Analysis of metabolic parameters showed that *db*/*db* mice with hypothalamic grafts had a nearly 20% reduction in body weight relative to mice with mock transplantation or cortical progenitor grafts in the hypothalamus. This effect was apparently due to an increase in energy expenditure because food intake remained elevated. Most strikingly, basal blood glucose was normalized to wild-type levels, although insulin levels remained high. These interesting results suggest multiple directions for neuronal transplantation to be used to probe principles of hypothalamic development and function. In addition, the technique is of interest as a possible strategy for treating obesity.

Neuronal transplantation offers a method to determine regional and temporal requirements for cell-type specification (Gaiano and Fishell, 1998). The hypothalamus is composed of a large number of intermingled, molecularly defined cell types with different functions that are grouped regionally into brain "nuclei." Judging by the electrophysiological characteristics that the authors report, the results are mostly consistent with regionally appropriate differentiation. At a molecular level, though, this is less clear. For instance, POMC and NPY neurons were found in the grafts, but it was not shown whether the differentiation of POMC and NPY neurons was limited to the arcuate nucleus, which is their location in the hypothalamus. The methods highlighted in this study could be further applied to investigate cell-type specification in the hypothalamus.

This work also has implications for examining hypothalamic circuit function. A fundamental but unresolved question that haunts hypothalamic neural circuit research is the mode of information transfer in these circuits. The authors suggest that leptin receptor-expressing hypothalamic neurons recapitulate a portion of the leptin-sensitive network for regulating body weight and glucose by sensing circulating leptin and signaling to leptin-blind portions of the network. More generally, though, neuron transplantation may yield insight about the necessity of precisely "wired" circuits that primarily use fast neurotransmitters in comparison to the role of volume transmission by neuropeptides. This is because grafts may not differentiate and incorporate into circuits in time for the "critical period" of leptin-dependent formation of certain hypothalamic circuits (Bouret et al., 2004). Furthermore, the exact placement of the transplanted cells will determine which leptin-sensitive circuits are formed. Although the axon projections of the transplanted neurons were not reported, future work could correlate the physiological effects of hypothalamic grafts with the presence or absence of particular circuits. For example, is the limited impact on body weight indicative of the importance of long-range wired transmission for this function? Conversely, in light of full normalization of glucose levels, is glucose regulation less sensitive to this critical period, or might this indicate a predominant role for local circuits or volume transmission? Notably, the observed physiological profile of neuronal transplantation is remarkably similar to virally mediated reactivation of leptin receptor signaling in the arcuate nucleus after the critical period, which led to a normalization of circulating glucose and a modest reduction in body weight (Coppari et al., 2005). Further analysis of neural circuits after postnatal rescue of leptin signaling could provide insight into the importance of wired circuits for specific hypothalamic functions.

What is the potential for the neuron transplantation approach described here to be used as an obesity therapy? Despite their striking results, the authors, in a podcast on the *Science* website, have tamped down expectations for this technique as a therapeutic approach. This is not simply due to the invasiveness of neuron transplantation; for example, deep-brain stimulation is under clinical investigation for obesity treatment (Halpern et al., 2011). Instead, one issue is that nearly all obese individuals have functional leptin receptors, but they exhibit leptin resistance. Therefore, it is unclear if leptin-receptor-expressing neurons transplanted into the hypothalamus of leptin-resistant subjects would have effects comparable to transplants in leptin-receptor-lacking *db*/*db* mice. Another issue is that implantation was performed in neonatal mice but obesity typically occurs later in development. It remains to be determined whether hypothalamic neural progenitors transplanted to juvenile and adult brains will have an impact on obesity and diabetes. Despite these uncertainties, though, it is also exciting to consider the new opportunities for possibly transplanting neurons engineered to express a transgene that permits selective pharmacological (Magnus et al., 2011) or optical (Zhang et al., 2007) manipulation of neural activity, which would allow the function of these populations to be more closely analyzed. Such modifications may also increase the functional efficacy and possibly enhance the clinical potential of hypothalamic grafts. It will be interesting to see how the application of this approach in the hypothalamus can enable new directions to reveal the operation of this complex and elusive brain structure.

REFERENCES

Bouret, S.G., Draper, S.J., and Simerly, R.B. (2004). Science *304*, 108–110.

Cohen, P., Zhao, C., Cai, X., Montez, J.M., Rohani, S.C., Feinstein, P., Mombaerts, P., and Friedman, J.M. (2001). J. Clin. Invest. *108*, 1113–1121.

Coppari, R., Ichinose, M., Lee, C.E., Pullen, A.E., Kenny, C.D., McGovern, R.A., Tang, V., Liu, S.M., Ludwig, T., Chua, S.C., Jr., et al. (2005). Cell Metab. *1*, 63–72.

Czupryn, A., Zhou, Y.D., Chen, X., McNay, D., Anderson, M.P., Flier, J.S., and Macklis, J.D. (2011). Science *334*, 1133–1137.

Gaiano, N., and Fishell, G. (1998). J. Neurobiol. *36*, 152–161.

Halpern, C.H., Torres, N., Hurtig, H.I., Wolf, J.A., Stephen, J., Oh, M.Y., Williams, N.N., Dichter, M.A., Jaggi, J.L., Caplan, A.L., et al. (2011). Acta Neurochir. (Wien) *153*, 2293–2306.

Kowalski, T.J., Liu, S.M., Leibel, R.L., and Chua, S.C., Jr. (2001). Diabetes *50*, 425–435.

Magnus, C.J., Lee, P.H., Atasoy, D., Su, H.H., Looger, L.L., and Sternson, S.M. (2011). Science *333*, 1292–1296.

Zhang, F., Wang, L.P., Brauner, M., Liewald, J.F., Kay, K., Watzke, N., Wood, P.G., Bamberg, E., Nagel, G., Gottschalk, A., and Deisseroth, K. (2007). Nature *446*, 633–639.

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., and Friedman, J.M. (1994). Nature *372*, 425–432.