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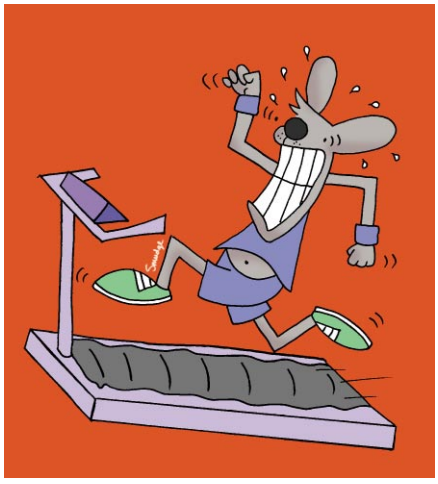
Are drug targets missed owing to lack of physical activity? ▼

The human genome, our book of life, is beginning to reveal its secrets, and the pharmaceutical industry is set to reap the projected crop of hundreds of new drug targets. Our genome's amazing simplicity, merely ~30,000 genes, and in particular its high similarity with the mouse genome, should make us humble. At the same time, it should support the cause for using mice and rats as animal models for human disease. Yet, the controversial public debate surrounding the use of laboratory animals in drug development is far from being resolved[1,2]. Without venturing into the moral and ethical aspects of this hot topic, I would like to present an intriguing but less familiar aspect of biochemical and pharmacological studies in laboratory rodents. Namely, the likelihood that constant deficit of physical activity of caged laboratory animals affects their CNS gene expression levels and consequently the interactions among gene products and the suitability of certain animal models for identifying the most favorable new drug targets.

Anyone using laboratory rodents in drug development research is aware that mice and rats are confined most of the time, often for the entire duration of the experimental protocols, to small cages that do not allow them to experience the levels of physical activity of wild rodents. Sizes of standard laboratory cages are typically about 40 cm × 5 cm × 18 cm for rats, and smaller for mice.



While such cages are approved by animal welfare authorities, clearly they do not allow the animals to run or climb as they would in the wild, and as their genes were fine-tuned to their physiology during millions of generations. Such conditions, putting aside issues of animal welfare, could be detrimental for drug development research because they might possibly obscure certain real-world situations by affecting gene expression and consequently interfering with the identification of drug targets.

Supporting data

The following examples should highlight my point. Expression of vasoactive intestinal peptide (VIP), a well-known survival factor for CNS neurons, was increased in the hippocampus of rats following a 60-min walk on an activity wheel[3]. Similar observations were made for the expression of galanin, another neurotrophic peptide, in the rat locus ceruleus following treadmill exercise[4]. Expression of another growth factor, brain-derived neurotrophic factor (BDNF), was elevated up to threefold in the dentate gyrus of rats following a 20-day period of voluntary physical activity through free access to running wheels[5]. Moreover, this increase was similar and additive with the increased BDNF expression in the dentate gyrus of rats treated with an antidepressant drug[5]. Notably, BDNF is implicated in brain plasticity mechanisms such as long-term potentiation and learning. Indeed, voluntary physical exercise for several weeks was shown to enhance learning in mice as evident from their performance in the Morris water maze, a popular spatial memory test[6,7].

As mice and rats are extensively employed in the development of new CNS drugs, such observations call for an urgent need to assess the effects of laboratory rodent caging and, in particular, the lack of physical activity on drug research. Specifically, it is likely that drug targets might be missed, or even worse, given too much significance, when based on studies in docile laboratory animals. Such animals might not correctly reflect the normal repertoire of CNS proteins, and hence could be inherently flawed for modelling certain human diseases. The increased favorable effect of an antidepressant drug on BDNF expression in physically active rats[5] illustrates that, in some cases, biological effects of drugs could be more pronounced in animals

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with free excess to treadmill exercise. The drug industry should pay more attention to this probable scenario.

Moreover, these notions are not restricted to CNS drug development. For example, short-term treadmill exercise training of rats was shown to improve myocardial tolerance to ischemia–reperfusion injury[8] and diaphragm antioxidant capacity[9]. Another striking example is given by a recent study in which rats were maintained for 12 weeks in specially designed raised cages that required them to rise to erect bipedal stance to eat and drink. These rats had significantly increased muscle and cortical bone mass in their tibias compared with control rats housed in standard laboratory cages[10].

The immune system is also more active in exercised rats compared with docile animals: voluntary exercise on running wheels for 5 weeks dramatically augmented *in vivo* natural killer cell toxicity[11]. Numerous studies demonstrate that exercised rodents are generally healthier, which is not surprising given the obvious advantages of physical activity in humans, and in view of the high similarity between the mouse and the human genomes[12].

Conclusions

The above examples illustrate that regular voluntary physical activity can alter various aspects of mouse and rat physiology that could be relevant for drug development. Clearly, more attention should be paid to such effects in the context of the quest for new drug targets. This cautionary note might be in particular valid for CNS drug development, but could also concern immune-related drug targets. Hippocrates, the founder of scientific medicine, wrote some 2400 years ago:

> Of all the causes which render the life of man short and miserable, none have greater influence than the lack of proper exercise.

The drug industry should take notice that this in all probability is also true for laboratory rodents, our distant mammal relatives.

Box 1. The outstanding questions

- How similar are mice and humans in their need for regular physical activity?
- To what extent is CNS gene expression modified in docile mice or rats compared with physically active laboratory rodents?
- Are changes in gene expression in active animals transient or long-lasting, and how do they affect the suitability of these animals to model human diseases?
- Could favorable CNS drug targets be missed by the routine use of inactive laboratory rodents?
- Will voluntary physical exercise allow laboratory rodents to be better animal models for human neurological and psychiatric diseases?
- Should running wheels be implemented in standard laboratory protocols for laboratory rodents in drug development research? What other measures could be applied to ensure that they are allowed the best levels of physical activity for serving as human disease models?

References

1 Malakoff, D. (2000) Animal research. Activists win big on rodent, bird rules. *Science* 289, 377

2 Ferry, J. (1999) New calls made for changes in research on animals. *Lancet* 354, 1978

3 Eilam, R. *et al.* (1999) Locomotor activity causes a rapid up-regulation of vasoactive intestinal peptide in the rat hippocampus. *Hippocampus* 9, 534–541

4 O'Neal, H.A. *et al.* (2001) Prepro-galanin messenger RNA levels are increased in rat locus coeruleus after treadmill exercise training. *Neurosci. Lett.* 299, 69–72

5 Russo-Neustadt, A.A. *et al.* (2000) Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic factor transcripts in the rat hippocampus. *Neuroscience* 101, 305–312

6 van Praag, H. *et al.* (1999) Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proc. Natl. Acad. Sci. U. S. A.* 96, 13427–13431

7 Anderson, B.J. *et al.* (2000) Exercise influences spatial learning in the radial arm maze. *Physiol. Behav.* 70, 425–429

8 Powers, S.K. *et al.* (1998) Exercise training improves myocardial tolerance to *in vivo* ischemia–reperfusion in the rat. *Am. J. Physiol.* 275, R1468–R1477

9 Vincent, H.K. *et al.* (2000) Short-term exercise training improves diaphragm antioxidant capacity and endurance. *Eur. J. Appl. Physiol.* 81, 67–74

10 Yao, W. *et al.* (2000) Making rats rise to erect bipedal stance for feeding partially prevented orchidectomy-induced bone loss and added bone to intact rats. *J. Bone Miner. Res.* 15, 1158–1168

11 Jonsdottir, I.H. *et al.* (2000) Enhancement of natural immunity seen after voluntary exercise in rats. Role of central opioid receptors. *Life Sci.* 66, 1231–1239

12 Gurwitz, D. (2000) Physical activity: good for your health, very good for your gene expression. *Clin. Genet.* 57, 249–251

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Gene therapy: will it deliver for RA? ▼

Rheumatoid arthritis (RA) is a debilitating disease associated with increased mortality. Chemically derived drugs are still considered as the primary treatment of RA. However, these treatments are only partially effective in controlling the progression of the disease and are associated with several side effects.

In the past decade, the results of biomedical research have increased our knowledge regarding the pathological processes that take place in rheumatoid joints, in particular, the role of cytokines. These findings led to the use of tumor

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