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Review

The hyperactive syndrome: Metanalysis of genetic alterations, pharmacological treatments and brain lesions which increase locomotor activity

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ABSTRACT

The large number of transgenic mice realized thus far with different purposes allows addressing new questions, such as which animals, over the entire set of transgenic animals, show a specific behavioural abnormality. In the present study, we have used a metanalytical approach to organize a database of genetic modifications, brain lesions and pharmacological interventions that increase locomotor activity in animal models. To further understand the resulting data set, we have organized a second database of the alterations (genetic, pharmacological or brain lesions) that reduce locomotor activity. Using this approach, we estimated that 1.56% of the genes in the genome yield to hyperactivity and 0.75% of genes produce hypoactivity when altered.

These genes have been classified into genes for neurotransmitter systems, hormonal, metabolic systems, ion channels, structural proteins, transcription factors, second messengers and growth factors. Finally, two additional classes included animals with neurodegeneration and inner ear abnormalities. The analysis of the database revealed several unexpected findings. First, the genes that, when mutated, induce hyperactive behaviour do not pertain to a single neurotransmitter system. In fact, alterations in most neurotransmitter systems can give rise to a hyperactive phenotype. In contrast, fewer changes can decrease locomotor activity. Specifically, genetic and pharmacological alterations that enhance the dopamine, orexin, histamine, cannabinoids systems or that antagonize the cholinergic system induce an increase in locomotor activity. Similarly, imbalances in the two main neurotransmitters of the nervous system, GABA and glutamate usually result in hyperactive behaviour. It is remarkable that no genetic alterations pertaining to the GABA system have been reported to reduce locomotor behaviour. Other neurotransmitters, such as norepinephrine and serotonin, have a more complex influence. For instance, a decrease in norepinephrine synthesis usually results in hypoactive behaviour. However, a chronic increase in norepinephrine may result in hypoactivity too. Similarly, changes in both directions of serotonin levels may reduce locomotor activity, whereas alterations in specific serotonin receptors can induce hyperactivity. The lesion of at least 12 different brain regions can increase locomotor activity too. Comparatively, few focal lesions decrease locomotor activity. Finally, a large number of toxic events can increase locomotor activity, particularly if delivered during the prepuberal time window. These data show that there is a net imbalance in the number of altered genes/brain lesions/toxics that induce hyperactivity versus hypoactive behaviour. Although some of these data may be explained in terms of the activating role of subcortical systems (such as catecholamines), the larger number of alterations that induce hyperactivity suggests a different scenario. Specifically, we hypothesize (i) the existence of a control system that continuously inhibit a basally hyperactive locomotor tone and (ii) that this control system is highly vulnerable (intrinsic fragility) to any change in the genetic asset or to any toxic/drug delivered during prepuberal stages. Brain lesion studies suggest that the putative control system is located along an axis that connects the olfactory bulb and the enthorhinal cortex (enthorhinal–hippocampal–septal–prefrontal cortex–olfactory bulb axis). We suggest that the increased locomotor activity in many psychiatric diseases may derive from the interference with the development of this brain axis during a specific postnatal time window.

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Contents

1. Introduction

Perhaps the most ancient record of a genetic manipulation is described in the Genesis, when Jacob, by putting striped branches in the troughs where the animals both drank and mated, was able to make them give birth to striped and spotted offspring [1]. In more recent times, the technology of transgenic mice has allowed the control of finer genetic changes, such as deletion, insertion or mutation of one single gene. Indeed, the recent introduction of a large number of such genetically engineered mice is an invaluable tool for the analysis of the relationship between genes and behaviour. An Internet source, in fact, lists at least 259 genes deleted, 1921 transgenic and 3203 targeted mutated animals realized until January 2008 (a total of 5283 different animals; see http://www.informatics.jax.org/imsr/IMSRSearchForm.jsp).

Some of these transgenic mice have been developed specifically to investigate the behavioural changes after mutation, deletion or insertion of a candidate gene into the genome. However, most of the transgenic animals are engineered to study gene–behaviour relationships: rather, many are used to test genetic influence on other processes, e.g. metabolic or hormonal systems. Regardless of the original aim that induced researchers to realize a transgenic model, most of the transgenic animals usually undergo behavioural phenotyping, and the resulting large amount of data is available to the scientific community in the form of incidental findings in papers.

Unfortunately, the systematic analysis of this large amount of data is difficult, because no comprehensive database is yet available. Specifically, a database of the behavioural phenotype of all transgenic mice would allow to address the study of gene–behaviour relationships from a completely new perspective: rather than testing what type of behaviour originates from the disruption of a candidate gene (classical approach), such a database would make it possible to reverse the question, thereby asking which animals, over the entire set of transgenic models, show a specific behavioural deficit (metanalytical approach). This approach can be defined as metanalytical, because, similarly to the metanalyses in medical research, all data from all available studies on transgenic animals are combined, to get a maximum amount of statistical information. This approach takes advantage of the analyses made on each transgenic mouse and allows understanding how many genes may be involved in the specification of a behavioural trait.

Moreover, to confirm that the genes thus identified are involved in the organization of the behavioural trait under study two additional strategies are here proposed: (i) the database deriving from genetic alterations must be compared with datasets deriving from pharmacological and brain lesion studies. In particular, starting from the entire set of pharmacological and brain lesion studies on rodent models (which is even larger than the transgenic dataset) the treatments producing the behavioural trait under study are selected; (ii) the entire dataset (genetic modifications, pharmacological treatments and brain lesion that produce a specific behavioural trait) must be compared with a similar database realized for a behavioural trait with opposite valence (e.g. high attention vs. low attention or, in the present case, hypoactivity vs. hyperactivity). This approach – the screening of the literature for animals with the increase or decrease of a specific behavioural trait after genetic, pharmacological and lesion interventions – is highly time-consuming but carries important informations about gene–behaviour relationships which might be applied to human genetic studies.

The present study analyses, as behavioural trait, the increase of locomotor activity in rodents. This behavioural trait is an optimal choice for a metanalytical approach, because behavioural phenotyping protocols usually include the analysis of locomotor activity. Therefore, a systematic analysis of the data from transgenic animals in the literature was carried out to organize a database of the genetic alterations linked to hyperactive phenotype. This database has been compared with all the pharmacological and lesion studies that produce increased locomotor activity. Finally, the entire process has been repeated for hypoactive animals. The comparison of these dataset allows showing unpredicted relationships between the genes and brain systems involved in hyperactive behaviour.