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Water Voles as a New Animal Model for Congenital Somatosensory Epilepsy

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Genetic studies of reflex epilepsy are conducted primarily on rodent strains in which seizures are triggered by audiogenic stimuli. The genetic aspects of somatosensory epilepsy induced by tactile stimuli remain unclear. Identifying genes that influence the development of seizures evoked by tactile stimuli is important for understanding the underlying mechanisms of somatosensory epilepsy, as well as for its prevention and treatment. This article summarizes previously published results from long-term population and laboratory studies, confirming the assumption of other authors that seizures induced by tactile stimuli are an element of antipredatory behavior that allows the preservation of genes predisposing to somatosensory epilepsy in natural populations. The genetic predisposition of water voles to handling-induced seizures has been shown to be associated with a coat color polymorphism controlled by the agouti locus. Thus, the water vole may become a promising object for genetic studies of somatosensory reflex epilepsy and understanding the evolutionary origins of this disease.

Keywords: agouti locus, antipredator behavior, *Arvicola amphibius*, avian predators, handling, population cycle, reflex seizures

先天性体性感覚てんかんの新たな動物モデルとしてのミズハタネズミ

反射てんかんにおける遺伝学的研究は、主に音刺激によっててんかん発作を引き起こすげっ歯類を対象に行われてきた。しかし、触覚刺激によって誘発される体性感覚てんかんの遺伝学的側面は未だ明らかになっていない。触覚刺激によって引き起こされるてんかん発作の発現に影響を与える遺伝子の特定は、体性感覚てんかんの潜在的なメカニズムを解明するとともに、本疾患の予防や治療においても重要である。本稿は、過去に発表された長期的な個体群研究および実験室での研究の結果を概括し、「触覚刺激によって誘発されるてんかん発作は野生個体群において捕食回避行動の一環であり、それによって体性感覚てんかんの素因となる遺伝子が維持されている」という他著者の仮説を裏付ける。ミズハタネズミにおけるハンドリング誘発性発作への遺伝的素因は、アグーチ遺伝子座によって制御される毛色多型と関連していることが示されている。このように、ミズハタネズミは体性感覚反射てんかんの遺伝学的研究、および本疾患の進化的な起源を理解するための有望な研究対象となる可能性を秘めている。

キーワード：アグーチ遺伝子座、捕食回避行動、ミズハタネズミ（*Arvicola amphibius*）、鳥類捕食者、ハンドリング、個体群サイクル、反射発作

Las Ratas Toperas como Nuevo Modelo Animal para la Epilepsia Somatosensorial Congénita

Los estudios genéticos sobre la epilepsia refleja se llevan a cabo principalmente en cepas de roedores en las que las crisis son elicitadas por estímulos audiogénicos. Los aspectos genéticos de la epilepsia somatosensorial inducida por estímulos táctiles siguen siendo poco claros. La identificación de los genes que influyen en el desarrollo de las crisis provocadas por estímulos táctiles es importante para la comprensión de los mecanismos subyacentes de la epilepsia somatosensorial, así como para su prevención y tratamiento. El presente artículo resume resultados previamente publicados de estudios poblacionales de largo plazo y de laboratorio, los cuales confirman la hipótesis planteada por otros autores de que las crisis inducidas por estímulos táctiles constituyen un elemento del comportamiento antipredatorio que permite la preservación, en las poblaciones naturales, de genes que predisponen a la epilepsia somatosensorial. La predisposición genética de los topillos de agua a presentar crisis inducidas por la manipulación está asociada con un polimorfismo en la coloración del pelaje controlado por el locus agouti. De esta forma, la rata topera puede convertirse en un modelo prometedor para los estudios genéticos de la epilepsia refleja somatosensorial y para la comprensión de los orígenes evolutivos de esta enfermedad.

Palabras clave: Locus agouti, comportamiento antipredador, *Arvicola amphibius*, depredadores aviares, manipulación, ciclo poblacional, crisis reflejas.

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The water vole, *Arvicola amphibious* (Linnaeus, 1758), belongs to the order Rodentia, the family Cricetidae, the subfamily Arvicolinae, and the genus Arvicola. It is a highly adaptable semi-aquatic herbivorous mammal that inhabits slow-moving rivers, streams, ponds, ditches, swamps, and wetlands. The range of the water vole extends from the Atlantic coast in Western Europe, reaching the Far Eastern region of Siberia and northwestern China, Iran, Iraq, northern Israel, the Caucasus, and Turkey. The body weight of adults is 140–260 g, the body length is 140–215 mm. Water voles live up to 3.5 years and maintain reproductive capacity throughout their live (Nazarova, 2013).

In the forest-steppe and subtaiga regions of the Western Siberia, populations of this species are subject to 1000-fold fluctuations with a period of 6–8 years (Evsikov et al., 1999). Population outbreaks cause significant damage to agricultural crops, pastures, and forests. To develop effective methods for population control, in 1979, a laboratory for population ecology and animal genetics was established at the Biological Institute of the Siberian Branch of the Academy of Sciences under the leadership of the institute's director, Professor Vadim Ivanovich Evsikov. New data on the life cycle, physiology, and behavior of the water vole were obtained in the laboratory.

Main Results of Population Research

Between 1980 and 2006, the main objectives of population studies were to investigate the influence of biotic and abiotic environmental factors on the physiological and behavioral characteristics of animals, as well as on the demographic and genetic structure of the population. Coat color, a visually detectable trait for which adaptive genetic polymorphism is conserved in the study population, was used as a marker of genetic variation. As with other authors (Nikolaeva, 1978), three main coat colors were identified: brown, black-brown, and black (Figure 1).

Figure 1

Coat Color Polymorphism in Water Voles.



Note. A – brown and black, B – dark-brown and black.

Brown water voles, the most common phenotype, are homozygous for the dominant wild-type allele of agouti (A). Individuals of the rare black phenotype, which constitute less than 7% of the population (Evsikov et al., 1997, 1999), are homozygous for the recessive allele of the nonaguti extreme gene (a^e), while dark brown voles are heterozygous (A/a^e) (Nasledova et al., 1980; Prasolova et al., 1991). The water vole has proven to be a very convenient model object for studying the genetic and physiological mechanisms underlying the regulation of population size and the adaptation of animals to regular environmental changes, due to the pleiotropic effect of agouti genes on fitness-related traits. The ratio of individuals of different color morphs has been shown to change periodically during the population cycle, which is explained by the different stress responses of brown, dark brown, and black individuals to biotic and abiotic environmental factors that affect their reproductive ability (Bazhan, 1991; Bazhan et al., 1996; Evsikov et al., 1999, 2001).

In 1982, a laboratory colony of water voles was established to study the long-term influence of living conditions at different phases of population dynamics on the physiological, behavioral, and reproductive characteristics of animals, as well as the role of olfactory communication in reproduction. From April to September, females and males were kept in pairs, and from October to March, they were kept singly. Voles captured during the years of population decline and depression (1982-1983) did not reproduce in the vivarium, which may be explained by the long-term negative impact of living conditions on reproductive function, as has been found in other vole species (Mihok & Boonstra, 1992).

The first mating resulting in the birth of viable offspring occurred only in 1984. Since then, the vivarium group has been regularly replenished with animals from wild populations to limit inbreeding. Mating pairs were selected based on a relatedness coefficient not exceeding 12.5%. Dates of birth and death, growth characteristics, age at sexual maturity, number of sexual partners, and reproductive success of each animal, assessed by the onset of estrus in females housed with a male, number of matings, parity, and litter size, were recorded. The animals' weight and body length were measured weekly until they reached 10 weeks of age, and then monthly. Males were assessed for aggressiveness and social dominance. Olfactory tests were conducted on both males and females.

The use of an integrated approach allowed us to obtain important information on the age-related changes in fertility and mortality, individual growth characteristics, timing of puberty, the ontogenesis of social behavior, genetic and maternal influences on reproductive capacity, social behavior, and survival of individuals. The obtained results revealed new genetic and physiological mechanisms of cyclical population dynamics (Evsikov et al., 2001; Nazarova & Evsikov, 2012).

Handling-induced Seizures in Water Voles

When conducting experimental studies, water voles had to be handled. This procedure caused seizures in some animals. Such cases were always recorded. The seizure usually developed within the first minute after the animal was handled. Typically, the seizure began with whisker twitching, facial tics, and blinking. This was followed by myoclonic jerking of the entire body, tonic tension, and rhythmic contractions of the muscles of the anterior body. The animal could arch its back, throw its head back, and grind its teeth. Some animals exhibited a “wild run.” In rare cases, clonic seizures spread to the entire body and were accompanied by loss of consciousness. Typically, the convulsions lasted no more than 1 min. After the seizure, the voles exhibited a period of postictal unresponsiveness lasting no more than 2 min. Less than 1% of animals had seizures that resulted in sudden, unexplained death.

Post-manipulation seizures were observed in 29.8% of individuals in the laboratory colony. The minimum and maximum ages of seizure onset were 39 and 1105 days, respectively; modal age – 189 days, median age – 274 days (Nazarova & Proskurnyuk, 2022). The development of a seizure was similar to the seizure pattern in a bank vole, *Myodes glareolus* (Schønecker, 2009) and meadow vole (*Microtus pennsylvanicus*) (Bronson & De La Rosa, 1994). Electrographic studies were not conducted, so the nature of the seizures remained unknown. Individuals with seizures were not excluded from reproduction.

Genetic Predisposition to Seizures

Pedigree analysis has shown that the proportion of offspring with seizures increases significantly if one or, especially, both parents were predisposed to them (Nazarova & Proskurnyak, 2022). In the "average parent"–"average offspring" groups, a significant positive correlation was found between the ages of onset of the first seizure, indicating that it is a heritable trait. Bronson and De La Rosa (1994) also found handling-induced seizures with a genetic component in wild-caught and laboratory-reared meadow voles. These data raise questions about the mechanism by which genes predisposing to seizures are maintained in natural rodent populations.

Predisposition to Seizures in Water Voles with Different Coat Colors

Approximately 70–80% of cases of epilepsy, a neurological disorder characterized by recurring seizures, are associated with one or more genetic factors (Hildebrand et al., 2013). Reflex epilepsy, characterized by seizures triggered by specific external stimuli, is a relatively rare subtype of epilepsy. Startle-induced seizures, a subtype of reflex epilepsy, can be triggered by a sudden and unexpected acoustic or tactile stimulus (Hanif et al., 2021). Reflex epilepsies can be accompanied by focal or generalized seizures. Identifying genes that trigger seizures is important for understanding the mechanisms underlying the development of seizure disorders.

Unlike audiogenic epilepsy, the genetics of tactile-induced startle epilepsy have not been studied (Dudko et al., 2023; Okudan & Özkara, 2018). The genetic predisposition to seizures induced by tactile stimuli may be explained by the pleiotropic influence of genes controlling coat color, since both melanocytes and nerve cells originate from the neural crest. Genes that control melanogenesis, such as MC1R (melanocortin-1 receptor, encodes by genetic loci *extension*) and agouti protein (encodes by genetic loci *agouti*), which influence the type of melanin production, are known to affect sensory sensitivity and nervous system excitability (Hoekstra, 2006). Mutations in the melanocortin-1 receptor that cause red hair color have been shown to have pleiotropic effects on sensitivity to thermal pain. People with red and blonde hair have lower pain sensitivity thresholds than dark-haired people (Li et al., 2016; Liem et al., 2005). Pain sensitivity also depends on the content and catalytic activity of tyrosinase, a key enzyme in melanogenesis and the synthesis of the dopamine precursor in melanocytes (Ono et al., 2017).

Interestingly, the agouti protein has structural similarities to venoms produced by snails and spiders, which paralyze prey within seconds by acting on neurotransmitter receptors or ion channels. It is believed that the primary function of the agouti protein is a direct effect on certain subtypes of Ca^{2+} channels (Manne et al., 1995). It has also been established that Ca^{2+} ions are involved in the regulation of neuronal excitability, and an imbalance of intracellular Ca^{2+} is a factor triggering the development of epilepsy (Rajakulendran & Hanna, 2016).

Research in psychology and neuroscience confirms that tactile stimuli can trigger a stress response and provoke seizures (DeGeorge & Metea, 2025; Harrold et al., 2024). In water voles and other rodents whose coat color is controlled by the agouti locus, the response to stress depends on the animal's phenotype (Bazhan et al., 1999; Bol'shakov et al., 1989). Studying the pleiotropic influence of genes controlling coat color on sensory sensitivity, stress response, and seizure development is important for understanding the evolutionary origins of reflex seizures and their genetics.

The relationship between coat color and seizure susceptibility was examined using available long-term individual data on water voles from a laboratory colony. Black water voles were classified as homozygous for the nonagouti extreme allele (Nasledova et al., 1980). The genotype of brown and dark-brown individuals was determined by analyzing pedigrees. Brown individuals, both of whose parents were brown, and whose offspring (and the litters in which the parents were raised) did not contain individuals with other coat colors, were considered homozygotes for the dominant gene of the agouti locus (AA). Heterozygotes (Aa^e) are non-black individuals who have one black parent or who have black offspring. Analysis of long-term data from breeding water voles revealed that coat color genes exert pleiotropic effects on the occurrence of seizures following manipulation. Among brown-colored voles, the proportion of those predisposed to seizures was significantly higher, than among dark-brown or black voles (Nazarova & Proskurnjak, 2024).

The Role of Reflex Seizures in Behavioral Defense Against Predators

The relationship between predator and prey is a fundamental aspect of ecology and evolution. The maintenance of coat color polymorphism in natural populations is usually achieved through balancing selection, which prevents the fixation or loss of any single-color morph. The camouflaging function of coat color or pleiotropic influence of coat color genes on the physiological and behavioral characteristics of water voles may contribute to the differential survival and reproduction of brown, dark-brown, or black individuals (Manne et al., 1995).

Stress induced by life-threatening predator cues affects the behavioral, physiological, and morphological characteristics of prey (Lima & Bednekoff, 1999). Since seizures can be considered as an element of the behavioral anti-predator repertoire (Chance & Russell, 1959; Fedotova et al., 2021), studying the influence of the agouti locus on survival in the natural environment is of considerable interest. It is suggested that seizures may disrupt the perception of the habitual ‘prey image’ and the stereotypical sequence of successful hunting behaviour and, therefore, increase the prey's chances of survival (Chance, 1957; Dixon, 1998; Driver & Humphries, 1970). The present study provides evidence that individuals with a genetic predisposition to seizures may have a selective advantage in high-predator environments. The water vole proved to be a convenient model for testing this hypothesis, since the periodic fluctuations in the numbers of this rodent are synchronized with the population dynamics of specialized, highly mobile birds of prey (Danilov, 1965; Weber et al., 2002). Predators catch the most numerous and accessible species. During population peak, the water vole accounts for 75–100% of the prey of the greater spotted eagle (*Clanga clanga*), black kite (*Milvus migrans*), hen harrier (*Circus cyaneus*), and common kestrel (*Falco tinnunculus*) (Danilov, 1976).

The results of population and laboratory studies showed that tonic-clonic seizures after handling were observed in 2.4% of water voles captured in the wild and kept in a vivarium for at least three months. In the sample of animals captured during the population decline period, the proportion of individuals with seizures was five times higher than among animals captured during the population peak period (Nazarova & Proskurnjuk, 2022). Since the predisposition to seizures is inherited, the increase in the proportion of water voles with seizures during population declines can be explained by positive selection of individuals that exhibited seizure behavior in the previous phase of the population cycle (peak), when pressure from raptors was very high. If a genetic predisposition to seizures is beneficial for survival and reproductive success during periods of high predator-prey population density, then genes responsible for seizures will persist in the population.

This conclusion was confirmed by comparing the ratio of individuals of different color morphs in a natural population of water voles and in the diet of raptors. The data used for the analysis were presented in publications by Nikolaeva (1978) and Danilov (1965). These authors conducted their research simultaneously and in the same area. Nikolaeva presented data on the ratio of water voles of different color morphs in the natural population, and Danilov presented data on these ratios in the prey of avian predators: the kite, the kestrel, and the owl. The main objective of Nikolaeva's study was to determine whether geographic variation in water vole coat color is related to the predominant soil color. She showed that coat color does not serve as camouflage, which contradicts the findings of authors who conducted studies on other rodent species (Hoekstra, 2006; Kaufman, 1974). An analysis of the data obtained by Nikolaeva and Danilov showed that the proportion of black individuals among the prey of raptors is significantly higher than in the wild population, while the proportion of brown individuals is lower, which indicates selective capture of black individuals by raptors. The proportion of dark-brown water voles in the prey of raptors corresponded to that in the wild population (Nazarova & Proskurnjak, 2024). Differential survival of individuals may be associated with physiological or behavioral traits on which coat color genes have a pleiotropic effect. Black water voles differ from brown water voles in that they are more resistant to stress (Makarova & Bazhan, 1999; Moshkin et al., 1990), which may explain their lower susceptibility to tactile signals that cause seizures. Perhaps for this reason, black individuals become easier prey for predators.

Unpredictable behavior, so-called “Prothean” behavior, makes hunting prey more difficult and therefore increases its chances of survival (Chance & Russell, 1959; Dixon, 1998; Driver & Humphries, 1970). In rodents, similar behavior includes catalepsy, a passive-defensive freezing response (Humphreys & Ruxton, 2018), and tonic-clonic seizures, that develop reflexively in response to acoustic or tactile stimuli (Bronson & De La Rosa, 1994; Poletaeva et al., 2017).

Why Has the Proportion of Animals with Seizures Increased Significantly in a Laboratory Colony?

The proportion of individuals in the natural population predisposed to seizures was less than 3%, but in laboratory colony it increased approximately to 30% (Nazarova & Proskurnjak, 2022). Between 1984 and 2006, the average proportion of individuals with seizures among voles born in the vivarium was 11.4% (n = 1331), and between 2007 and 2025 it increased sharply to 53.6% (n = 900). The sharp increase in the proportion of individuals with seizures coincided with the completion of long-term population studies in 2006. After 2006, to limit inbreeding, only a small number of wild individuals were captured every 1–3 years and introduced to laboratory-reared water voles. Water voles predisposed to epileptic seizures lived longer, than those without this predisposition, and were therefore able to produce more offspring (Nazarova & Proskurnyak, 2022). Therefore, the increase in the proportion of individuals prone to seizures may be associated with an increase in the frequency of genes controlling the onset of handling-induced seizures in the laboratory colony.

On the other hand, it is known that stress is a natural factor that can trigger seizures (DeGeorge & Metea, 2025). Glucocorticoids and corticotropin-releasing hormone affect excitatory and inhibitory processes in the areas of the brain involved in the development of seizures. Through epigenetic regulatory mechanisms, prenatal and early postnatal stress associated with body weight measurements in pregnant and lactating females may influence the development of the hippocampus, the hypothalamic-pituitary-adrenal axis, neuroplasticity, and the development of handling-induced seizures in the offspring (Chen et al., 2017; Huang, 2014).

To summarize the previous results, it should be noted, that in a population of water voles with cyclic population dynamics, there are individuals that are genetically predisposed to seizures caused by tactile stimuli. After the population peak, the proportion of such individuals increased, indicating that under high predation risk conditions, the relative fitness of individuals susceptible to seizures is higher than that of individuals without seizures. Since this trait is heritable, successful selection for a predisposition to seizures is possible if they increase survival.

Water Vole as a Perspective Object for Biomedical Research

Understanding the evolutionary history of seizures and their adaptive significance is important for developing measures to prevent and treat epilepsy. The goal of medicine is to find and treat the cause of disease, not the symptom. In 1942, Temple Fay noted that a convulsive reaction could be induced in any animal and proposed a theory to explain the origin and adaptive significance of seizures in vertebrates. The typical seizure pattern in terrestrial vertebrates—torsional twisting, back extension, and repetitive flexion-extension movements—is characteristic of the motor development level of amphibians. A typical set of convulsive movements, a “defensive reflex” that has been preserved in humans, apparently helped ancient amphibians avoid the dangers associated with life on land and return to the water (Doman & Pelligra, 2003; Fay, 1942).

Currently, genetic research on reflex epilepsy is primarily conducted using rodent strains sensitive to audiogenic stimuli (Garbuz et al., 2022). Only recently, Swain et al. (2023) proposed a selectively bred line of prairie voles (*Microtus ochrogaster*) as an unconventional animal model to study the development of genetically acquired epilepsy induced by manipulation. Voles from this strain exhibit heritable, adult-onset, handling-induced seizure behavior. However, the genes predisposing to tactile-induced epilepsy remain unknown (Okudan & Özkara, 2018). The water vole may be a valuable subject for genetic studies of somatosensory reflex epilepsy, since predisposition to seizures is associated with genetic polymorphisms in coat color.

As with other forms of reflex epilepsy, somatosensory-evoked reflex seizures may be caused by abnormal neural hyperexcitability in response to specific sensory cues. It is known that the skin is the main organ sensitive to external stress factors. Coat coloration, controlled by the agouti locus, and stress response have been shown to be interrelated in water voles and other rodent species (Bazhan, 1991; Bol'shakov et al., 1989; Hayssen et al., 2002). Through localized production of neuroimmunomodulators and catecholamines, the skin can initiate the transmission of stress signals to the brain (Paus et al., 2006; Slominski et al., 2012). The agouti gene, encoding the agouti signaling protein (ASIP), a paracrine inhibitor of melanocyte-stimulating hormone on melanocortin receptors of pigment and other cells, has pleiotropic effects on many physiological processes (Ducrest et al., 2008; Manne et al., 1995) and may be a promising candidate for studying the genetic mechanisms of reflex epilepsy caused by sudden stressful tactile stimuli. Mutations in the non-coding region of the agouti gene are responsible for skin and hair color in humans (Kanetsky et al., 2002). The human agouti-related protein (AgRP) is highly similar to ASIP (Wilson et al., 1995). The AgRP signaling pathway involves GABA – an inhibitory neurotransmitter – and the melanocortin system in the brain, which may influence seizure susceptibility, but the link between the agouti gene and epilepsy has not yet been studied.

In conclusion, the use of outbred water voles with polymorphic coat color as model animals in experimental neurophysiological studies opens new opportunities for identifying risk genes for manipulation-induced epilepsy, new drug targets, and successful modeling of human neurogenetic disorders.

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