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Telemetry Physical Activity Monitoring in Minipig's Model of Huntington's Disease

Monitoring fyzické aktivity u miniprasečího modelu Huntingtonovy nemoci

Abstract

Animal models represent a key tool for Huntington's disease (HD) research. During the last decade large animal models of HD have been established to improve knowledge of HD under large brain conditions. Transgenic minipig expressing N-terminal part of human huntingtin with 124 CAG/CAA repeats seems to be very promising HD model. Its previous characterization has shown various phenotypes affecting subcellular, cellular as well as organ systems level. The goal of this study was to detect and analyze a pathological pattern in physical activity of transgenic (TgHD) boars at the age of three years using telemetry approach. Into the study we have included five TgHD and five wild type (WT) animals for comparison. The physical activity was measured by the telemetric system rodentPACK2 whereas transmitter was placed into the collar. The analysis have shown significant decrease of total acceleration representing physical activity in TgHD boars between 4:40 and 5:30 a.m. (after night sleep – before morning feeding) in comparison with WT ones which could be explained with disturbed energy metabolism. Telemetry approach will play an important role in the study of physical activity and biopotentials essential for deeper characterization of large animal HD models in their preclinical and clinical phase.

Souhrn

Zvířecí modely představují klíčový nástroj pro studium Huntingtonovy nemoci (HN). V posledním desetiletí byla snaha vytvářet velké zvířecí modely této choroby z důvodu zlepšení znalostí o patologických změnách v mozku, který se co nejvíce podobá lidskému. Transgenní miniprase exprimující N-terminální část lidského mutovaného huntingtinu se 124 CAG/CAA repeticemi se zdá být velmi nadějným modelem pro studium HN. Jelikož předchozí charakterizace tohoto modelu prokázala rozličné fenotypy postihující subcelulární, buněčnou stejně tak i orgánově-systémovou úroveň. Cílem této studie bylo detekovat a analyzovat patologický vzorec ve fyzické aktivitě transgenních (TgHD) kanců ve věku 3 let pomocí telemetrie. Do experimentu bylo zařazeno pět TgHD a pro srovnání pět netransgenních (WT) kanců. Fyzická aktivita byla u kanců měřena pomocí telemetrického systému rodentPACK2, přičemž transmiter byl umístěn do límce na krku. Na základě analýzy bylo zjištěno signifikantní snížení totálního zrychlení reprezentujícího fyzickou aktivitu u TgHD kanců mezi 4:40 a 5:30 ráno (po nočním spánku – před ranním krmením) v porovnání s WT jedinci, které může být vysvětleno narušeným energetickým metabolizmem. Telemetrická analýza bude jistě hrát v budoucnosti významnou roli ve studii fyzické aktivity a biopotenciálů důležitých pro podrobnější charakterizaci preklinické a klinické fázi HN u velkých zvířecích modelů.

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Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.
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Key words

Huntington's disease – minipig – telemetry – collar – physical activity – acceleration

Klíčová slova

Huntingtonova nemoc – miniprase – telemetrie – límec – fyzická aktivita – akcelerace

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Aim of the study

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by polyglutamine expansion mutations in the huntingtin protein [1].

There is no cure or effective treatment for HD, and death typically occurs 15–20 years after the onset of HD motor symptoms. Patients with HD progressively develop symptoms of clinical psychiatric disorders, cognitive deficits, dementia and physical disability [2,3]. Mutated huntingtin action as well as loss of wild type huntingtin function affect not only the brain structures but also peripheral tissues or organ systems like testes, heart, pancreas, skeletal muscle, etc. [4–7]. Deficits in sleep and circadian organization have been identified as common early features in patients with HD that correlate with symptom severity and may be instrumental in disease progression. These observations were also detected in the most employed mouse model (R6/2) [8] or ovine model of HD [9]. Importantly heart disease has been attributed as a major cause of death in patients with HD. In addition R6/1 mice exhibited profound autonomic nervous system cardiac dysfunction involving both sympathetic and parasympathetic limbs associated with altered central autonomic pathways leading to cardiac arhythmias and sudden death [2].

The long-term collection of neurobehavioral and other physiologic data using telemetry devices represents a critical component of differently focused animal studies. Such devices have to be implanted in a location that is safe, well-tolerated, and functional. Göttingen minipigs (*Sus scrofa domesticus*) represent an ideal large animal model for biomedical studies due to their relatively small size, characterized health status, and ease of training and handling [10]. Moreover Yorkshire pigs were also used in long-term, simultaneous telemetric monitoring of blood flow, pressure and heart rate in heart failure models [11]. EEG, ECG, activity and core temperature monitoring were successfully measured in HD mouse models (R6/2 and R6/1) by telemetry devices [2,8].

The aim of study was to find and measure the physical activity disturbances characterized by deficit in sleep and circadian organization of transgenic (TgHD) minipigs expressing human mutated huntingtin in comparison with wild type boars (WT) by telemetry approach. The next goal of present study was to develop automatic system for measurement and evaluation of physical activity in minipigs.

Methods

Minipigs

All experiments were conducted with the approval of the State Veterinary Administration of the Czech Republic and in accordance with Czech regulations and guidelines for animal welfare.



Fig. 1. The positioning of the collar for activity measurement in TgHD boar.

The transgenic line founder sow "Adela" expressing N-terminal part of human mutated huntingtin with 124CAG/CAA [12], born July 2009, as well as her offsprings (F1, F2, F3 and F4) are without clinical symptoms of HD at the present time. However, until now several phenotypes like the reduced male reproductive parameters (e. g. fewer spermatozoa per ejaculate), impaired mitochondrial function in spermatozoa [13], lower level of total creatine in the brain [14], decrease of relative phosphodiester concentration in testicular parenchyma [15] and blood serum cytokine imbalance [16] have been detected. We expect the onset of the HD related clinical symptoms in the second half of their life, i.e., after the 10th year. Transgenic boars from F2 generation (3 years old) before HD onset (n = 5) and control WT siblings (n = 5) we used for telemetry study. The boars were individually held in the neighboring boxes (all together in one part of the stable).

Telemetric system

In the experiments we used the telemetric system rodentPACK2 obtained from emka TECHNOLOGIES (France). RodentPACK2 has been primarily designed for rodent studies. This fact has forced us to newly develop prototype equipment interconnecting connectors screwed to external transmitters with internal electrodes for biopotentials and temperature measurement fixed into the minipig's body possessing high durability. Telemetric system consists of small transmitters and central receivers. Every transmitter can acquire and transmit four biopotencial signals and/or core temperature in combination with x, y, z and total acceleration. The measurements can be synchronized with video record (infrared cameras). We have performed some minipig pilot experiments (EEG, ECG, EEG, temperature measurement) complicated with secondary infection and now we have design a new type of mounting approach that will be tested in close future. In present study the acceleration channels have been used only. Data were acquired at sampling frequency 100 Hz with resolution ± 2 g. In the learning period (before activity measurement) the minipig boars have obtained the empty collars (Fig. 1).

Moreover if the measurement was not running, minipigs still wore the empty collars. It eliminates the collar influence on their behavior. Minipig boars wore a collar with

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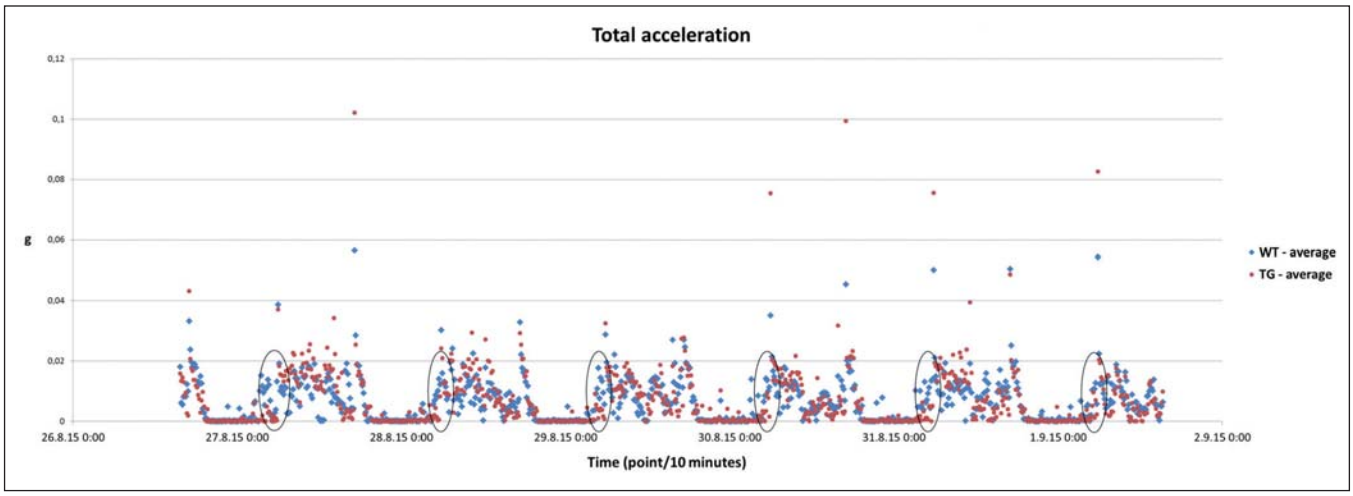


Fig. 2. Total acceleration (gravity acceleration – m/s^2) representing physical activity of TgHD and WT animals over six following days.

Each point (blue – WT, red – TgHD) represents averaged total acceleration of five animals (TgHD or WT) from 10 min sampling. The ellipses display mark time periods (4:40–5:30) in individual days.

transmitter during experiment. The measurement sessions started in the morning and ends afternoon. There was minimally one whole day (two nights) between start and end of the session. Period between individual sessions was approximately one month. All events during the measurement session were recorded e. g. time of feeding, cleaning, veterinary and zootechnician intervention or other activities.

Data analysis

For the statistical analysis we have used the last session including majority of days during weekend without unusual disturbing activities. We have decided to analyze the part of day – early morning just before staff coming after night (before morning feed) – which is hypothetically daily time with minimal external influences. For data analysis we have used two software provided by emka TECHNOLOGIES – iox2 for data acquisition and real-time analysis as well as ecgAUTO for complex analysis. Total acceleration (gravity acceleration – m/s^2) representing physical activity of animal was processed in ecgAUTO software. The total physical activity was sampled at 100 Hz and averaged over 10 min. Generated physical activity (mean from 10 min) from five TgHD and five WT boars were consequently averaged and used for statistical analysis. This simple algorithm for the comparison of WT and TgHD boars' physical activity was used for different daily time whereas sophisticated signal processing will be prepared in close future.

Statistics

A level $p < 0.05$ was considered as a statistically significant difference. For statistical analysis of total acceleration of TgHD and WT group between 4:40 and 5:30 a. m. a one-way ANOVA test with Bonferroni's multiple comparison post-test were employed using GraphPad PRISM software (GraphPad Software, San Diego, CA, USA).

Results

The analysis of total acceleration values from TgHD and WT animals showed similar distribution pattern over several days (Fig. 2). The minimal activity of animals was detected during the night from 19:00–19:30 to 3:00–3:30. This time period is generally connected with no human activity in the stable. The staff for morning feeding is coming about 5:00 into the stable with starting of feeding about 5:35–5:45. Next activity of animal is associated with cleaning procedure (7:00–9:00) whereas animals are obtaining new straw as a bedding that serves also as a tool for next activity until 11:00 (the time when the staff is leaving the stable). It is in accordance with decrease of animal activity between 11:00 and 13:00. Afternoon the staff is coming again about 15:00–15:30 with starting of feeding between 16:40–17:20. Immediately after afternoon feeding the feedboxes are cleaned and the staff is leaving the stable about 18:00. This organization pattern forced us to choose the daily period which would be minimally affected by external factors. Thus we have focused on the period after long night sleep just before morning feeding. The analysis of this time interval (4:40–5:30) showed decrease of mean total acceleration of TgHD boars compared to WT one during all six days of session. Although three differences weren't statistically significant the rest of differences in 28th, 29th and 31st August 2015 were (Fig. 3).

Conclusion

In this study we have described six days lasting telemetry session in which we have recorded physical activity of TgHD and WT minipigs. We have successfully measured and analyzed data as well as performed pilot analysis. Analysis of daily period from 4:40 to 5:30 showed significant decrease of total acceleration in TgHD animals in comparison with WT ones. This data suggest that 3 years old transgenic animals expressing human mutated huntingtin more slowly "starting" everyday faced with wild type siblings. We can hypothesize that this observation could be in agreement with our previous study [14] that revealed significant decrease of total creatine (tCr) in the thalamus of TgHD boars (2 years old) measured by 1H magnetic resonance spectroscopy. There were also detected other significant changes in metabolite ratios (increased metabolic ratios tCho/tCr in the striatum, thalamus, hippocampus as well as white matter) and we had supposed that the majority of the observed changes were predominantly related to changes in energy metabolism caused by decrease of tCr in TgHD. Creatine represents an important marker for brain energy metabolism. Lower crea-

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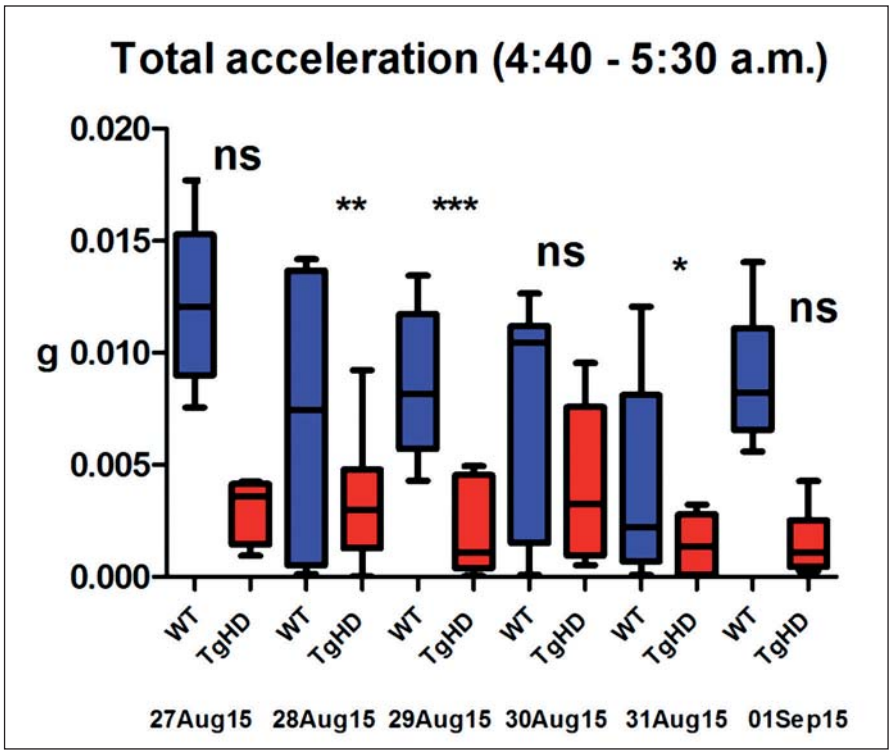


Fig. 3. Total acceleration of TgHD and WT animals between 4:40–5:30 a.m. during six following days.

Each column (blue – WT, red – TgHD) represents averaged total acceleration of five animals (TgHD or WT).

tine levels were reported in striatum of HD patients suggesting impaired energy metabolism [17]. Our data are also in accordance with data obtained from ovine transgenic model of HD expressing full length of huntingtin. The authors detected circadian behavioural abnormalities in young HD sheep that worsened with age. This change was a disturbed evening behaviour reminiscent of 'sundowning' depending upon their social grouping. That is seen in some patients with dementia [9].

The telemetric system uses accelerometer for physical activity monitoring. The big advantage of this system is monitoring of transgenic minipigs in their natural environment, without disturbing the study conditions. The system needs only minimal maintenance and has satisfactory resistant against aggressive environment in stable.

Telemetric monitoring of physical activity as well as other biopotentials (EEG, ECG, EMG, temperature, etc.) could reveal motoric, behavioral and sleep abnormalities of TgHD minipigs related to HD. In future we plan to repeatedly confirm presented data and focus on analysis of physical activity and biopotentials of TgHD and WT boars in other day periods, mainly in the night for complex sleep analysis. More powerful and sophisticated algorithms will be developed as well.

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