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Rat modeling and uric acid sustainability in hyperuricemic rats caused by potassium – oxonate.

Modelado en ratas y sostenibilidad del ácido úrico en ratas hiperuricémicas causadas por oxonato de potasio.

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ABSTRACT

Hyperuricaemia is an important risk factor of CKD, metabolic syndrome and cardiovascular disease. We aimed to assess that for how much time uric acid levels sustains in wistar rats. A hyperuricemia mouse model was to be established by potassium oxonate (PO) administered by oral gavage and by intraperitoneal injections. In hyperuricemia rats, serum uric acid levels increased but not significantly after oral administration for 7 days but administering PO intraperitoneally serum uric acid levels increased significantly after 1 hour but again returned within normal range after 2 hours. This paper presents method suitable for experimental hyperuricemia mouse model and shows the time feature of uric acid sustainability.

Keywords: hyperuricemia, rat model.

RESUMEN

La peruricemia es un factor de riesgo importante de ERC, síndrome metabólico y enfermedad cardiovascular. Nuestro objetivo era evaluar cuánto tiempo se mantienen los niveles de ácido úrico en ratas wistar. Se iba a establecer un modelo de ratón con hiperuricemia mediante oxonato de potasio (VO) administrado mediante sonda oral y mediante inyecciones intraperitoneales. En ratas con hiperuricemia, los niveles séricos de ácido úrico aumentaron, pero no significativamente, después de la administración oral durante 7 días, pero al administrar VO por vía intraperitoneal, los niveles séricos de ácido úrico aumentaron significativamente después de 1 hora, pero nuevamente regresaron dentro del rango normal después de 2 horas. Este artículo presenta un método adecuado para el modelo experimental de ratón con hiperuricemia y muestra la característica temporal de la sostenibilidad del ácido úrico.

Palabras clave: hiperuricemia, modelo rata.

INTRODUCTION

The incidence of hyperuricemia is increasing as people's living standards improve and their diets change. A large number of clinical research findings indicate that hyperuricemia is linked to cardiovascular disease and chronic renal failure. As a result, basic research into anti-hyperuricemic drugs is critical to preventing the occurrence and progression of these disease

Hyperuricemia can cause uric acid deposition in renal tissue, which can result in acute kidney injury (AKI). AKI was characterised by renal tubule dilation, inflammatory cell infiltration, the absence of visible boundaries between adjacent proximal tubule cells, and cell necrosis. The main cause of hyperuricemia is an increase in uric acid production, which can be caused by genetic factors or by consuming an excessive amount of purine precursors in the diet.

Urinary acid excretion default is another significant pathological change in hyperuricemia. To date, allopurinol and febuxostat have been used to inhibit excessive UA production with excellent therapeutic results. The kidney is the most important organ for UA excretion. Clinically, the most common causes of hyperuricemia are insufficient UA excretion in the kidney, decreased UA secretion transporter activity, and increased reabsorption transporter activity. However, drugs that improve UA excretion are uncommon. Animal models are crucial in the basic research of UA regulatory substances. Zebrafish , birds (hawk and broiler) , pig, tree shrew and mouse have all been used as experimental animals.

Mice and rats are the most commonly used among them for practical and economic reasons, as well as species differences with humans.

According to the literature, potassium oxonate (PO) (an uricase inhibitor) with or without high purine food is commonly used to induce hyperuricemia in rats/mice, but the experimental protocols vary. For example, the modelling period was 7 or 14 days, the PO was administered orally or intraperitoneally , the PO dose was 200 , 250 , or 300 mg/kg , and so on. The administration time is not consistent, resulting in a large difference in the data collected by different research groups, with some contradictory results.

Animal models are useful for pilot screening of antihyperuricemic agents and preliminary investigation of mechanism of action. To better understand the time-feature of the hyperuricemia mouse model, we administered PO orally to rats for 14 days. Changes in bodyweight, food and water intake, and serum uric acid levels were detected at various time intervals. This study suggests that when PO was used to create an efficient rat model, SUA levels were not maintained for a long time.

METHODOLOGY

REAGENT: Potassium Oxonate was purchased from Chennai based pharmaceutical company.

IN –VIVO EXPERIMENT: *In-vivo* study procedure and laboratory animal care protocols were strictly followed according to the guidelines of the animal care committee. The *in-vivo* experimental protocol was approved by the Animal Ethics Committee. Wistar rats either sex was taken for the study.

TEST ANIMALS: Wistar rats weighing 170–200 g were selected for the study. Animals were obtained from the animal house of the Department of Pharmacology, Bharati Vidyapeeth Medical College, Pune. All animals were housed in the animal house. Animals were allowed at least one week to adapt to the environment before the experiment gets started. These were housed 4 per cage under the schedule of 12 hours light and 12 hours dark. Animals were housed at 22 ± 2°C room temperature with 56 ± 5% relative moisture or humidity. Animals were given standard chow and clean water *ad-libitum*. Animals were kept in polycarbonate cages.

EXPERIMENTAL APPROACH: Potassium oxonate, a uricase inhibitor, was used to induce hyperuricemia in the rat model as described. Intra-peritoneal injection of potassium oxonate was given to rats at a dose of 200 mg/kg, 250 mg per kilogram (kg) body weight (b.w.) once a day for 7 da

ESTIMATION OF INITIAL SERUM URIC ACID LEVELS: The blood samples were collected from each rat through retro-orbital and given to a lab for estimation of uric acid.

EXPERIMENTAL DESIGN-

STUDY 1-

GROUP 1- treated with PO at dose of 200mg/kg body weight

GROUP 2- treated with PO at dose of 250 mg/kg body weight

RATS	BASELINE SUA	AFTER 1 WEEK SUA	AFTER 2 WEEKS SUA
H1	2.9	1.9	3.1
B1	4.19	2.7	4.05
T1	4.0	5.1	5.1
HB1	3.01	5.3	3.07
H2	1.98	5.4	7.5
B2	2.16	6.2	3.9
T2	2.6	2.8	0.07
HB2	3.1	3.4	3.07

There was no significant increase in the uric acid levels so we switched to the IP mode to see that if there is rise in SUA above normal range.

STUDY 2- Intra –peritoneal injections were given at the dose of 300mg/kg body weight in the same animals of group 1 taking interval of 2 weeks

RATS	BASELINE SUA	SUA AFTER 1 HOUR	SUA AFTER 3 HOURS
H1	1.9	12.5	6.7
B1	2.7	12.1	5.6
T1	5.1	15.3	5.2
HB1	5.3	15.2	5.3

In this study it was inference that the serum uric acid levels came witin normal range in the interval of 3 hours after administration of PO intraperitoneally in the dose of 300mg/kg body weight.

DISCUSSION

In this study, inducing hyperuricemia using potassium oxonate was able to produce hyperuricemia but not significantly and in case of administration intraperitoneally it was able to show significant rise but SUA were not sustained more than 1 to 1.5 hours. In addition to this these findings will support the need of additional studies to establish a more useful model for understanding the profile and efficacy of hyperuricemic drugs.

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