Urine formation begins with glomerular filtration, that is, the transport of filtered substances from glomerular capillaries to the Bowman’s capsule. The glomerular filtration barrier consists of the fenestrated endothelium of capillaries, basal membrane covering the external surface of capillaries, and podocytes. The foot processes of podocytes with interweaving finger-like processes are in close contact with the basal membrane and form slits and slit diaphragms performing filtration. The disturbances in the structure of podocytes and the interaction between their foot processes and the basal membrane result in the loss of functionality of the filtering apparatus [1] and, consequently, in the respective kidney diseases.

TRPC6 protein is a member of the family of TRPC (transient receptor potential canonical) channels expressed in different organs, including heart, brain and kidney, where these channels are involved in the transport of cations to specialized cells. The critical significance of TRPC6 localized in the podocytes for regulation of glomerular functions and, accordingly, for formation of the glomerular filtrate has been shown in several laboratories. It has been found that certain mutations of the gene encoding this channel result in the development of family focal segmental glomerulosclerosis (FSGS) [2–4]. Figure 1 shows the normal morphology of rat glomeruli (Fig. 1a) and the morphology with the typical signs of this disease developed as a result of hypertension induced by a high salt diet (Fig. 1b). Histology reveals the regions of sclerotication within the affected glomerulus and fusion of the glomerulus with the wall of Bowman’s capsule. In the Dahl SS (Salt-Sensitive) rats used to obtain Figure 1, hypertension and the associated kidney diseases are developed within a few days feeding a high salt diet. This rat strain is successfully used for studying various cardiovascular and kidney diseases [5–8].

Non-steroid anti-inflammatory drugs (NSAIDs) are extensively used in medicine and scientific...
research as inhibitors of the cyclooxygenase pathway of arachidonic acid metabolism. In clinical practice, they are used for the states associated with acute and chronic inflammation, pains, and decrease in blood coagulation. In addition, the role of NSAIDs in additional therapy for FSGS has been shown [9, 10]. However, the precise mechanism of their action is still unclear. Moreover, NSAIDs are rather rarely used for the treatment of kidney diseases as they cause various side effects.

Previously it has been shown that NSAIDs can influence the activity of different types of ion channels [11–13]. In addition, their effect on the activity of kidney ion channels has been described, including the regulation of epithelial sodium (ENaC), potassium and chloride channels [14–16]. Recently, after developing the new approach to registration of ion currents in the podocytes of isolated native rat glomeruli, we have described the decrease in the activity of TRPC channels under the influence of NSAIDs. Using the patch-clamp method, we have shown that the two structurally independent NSAIDs (diclofenac and ibuprofen) have significant inhibitory effects on the native TRPC channels in the podocytes of isolated glomeruli [17]. However, due to the absence of specific blockers of TRPC channels, our studies ex vivo do not allow us to exactly determine the channel specificity. Since we and other researchers [17–19] have shown that several types of TRP channels, including TRPC3 and TRPC6, are expressed in the podocytes, our task was to study the short- and long-term effects of NSAIDs on TRPC6 channels. In addition, we used the mutant variant TRPC6P112Q. Substitution of proline 112 for glutamine in the channel structure was described in FSGS patients. This mutation results in enhancement of channel activity in the plasma membrane and increase in angiotensin-dependent calcium current. It was also shown that the basal and carbachol- and angiotensin II-stimulated activity of the mutant channel expressed in HEK-293 cells in the whole-cell experiments was much higher than that of the wild type channel [4]. The measurement of intracellular calcium concentration in transfected cells revealed much more intensive increase in calcium concentration in response to carbachol stimulation of the cells transfected with the mutant protein TRPC6P112Q, compared to the cells transfected with the wild type channels. Ion current registration showed that the application of diclofenac (500 µM) caused suppression of the activity of single TRPC6 channels in several minutes. Preincubation with diclofenac also reduced the integral current through the membrane of CHO cells expressing TRPC6P112Q. Thus, NSAIDs reduce the current both through the wild type TRPC6 channels and through the mutant channel typical for the hereditary form of FSGS.

MATERIALS AND METHODS

Histological examination of glomeruli. The glomerular morphology typical of FSGS was demonstrated in Dahl SS male rats. The rats of this line are genetically predisposed to high arterial pressure at high sodium content in the feed [20, 21]. The 8–week-old rats from