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The intrinsic factor-vitamin B12 receptor and target of teratogenic antibodies is a megalin-binding peripheral membrane protein with homology to developmental proteins: Keys to renal toxicity, hypertension and Imerslund-Grasbeck syndrome

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The present report shows the molecular characterization of the rat 460 kDa epithelial glycoprotein that functions as the receptor facilitating uptake of intrinsic factor vitamin B12 complexes in the intestine and kidney. The same receptor represents also the yolk sac target for teratogenic antibodies causing fetal malformations in rats. Determination of its primary structure by cDNA cloning identified a novel type of peripheral membrane receptor characterized by a cluster of eight epidermal growth factor type domains followed by a cluster of 27 CUB domains. In accordance with the absence of a hydrophobic segment, the receptor could be released from renal cortex membranes by non-enzymatic and non-solubilizing procedures. The primary structure has no similarity to known endocytic receptors but displays homology to epidermal growth factor and CUB domain proteins involved in fetal development, e.g. the bone morphogenic proteins. Electron microscopic immune-gold double labeling of rat yolk sac and renal proximal tubules demonstrated sub-cellular co-localization with the endocytic receptor megalin, which is expressed in the same epithelia as the 460 kDa receptor. Furthermore, megalin affinity chromatography and surface Plasmon resonance analysis revealed a calcium dependent high affinity binding of the 460 kDa receptor to megalin, which thereby may mediate its vesicular trafficking. Due to the high number of CUB domains, accounting for 88% of the protein mass, we propose the name cubilin for the novel receptor. Ligands include renal toxins such as gentamicin and heavy metal carrying metallothioneins, angiotensin 1-1 and 1-8. Genetic defects in cubilin are the basis for Imerslund-Grasbeck syndrome.

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Nalbuphine hydrochloride extended release PK in hemodialysis patients and pruritus

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Uremic pruritus is a common and deleterious condition among hemodialysis (HD) patients and is known to affect about up to 50% of patients with renal failure and often causes long term pain and suffering. It is a distressing problem for the patients and is independent of gender, age, ethnicity, types of dialysis and the etiology of the underlying renal disease; among the factors causing pruritus in ESRD, the accumulation of uremic toxins, systemic inflammation, cutaneous xerosis and common comorbidities e.g., diabetes mellitus and viral hepatitis. Currently, there are no approved treatments in the United States or Europe. Uremic pruritus is typically treated with creams, antihistamines, ultraviolet radiation and the off-label use of various drugs, including opioids with limited success. To date, uremic pruritus remains an unresolved problem with renal transplantation being the only effective treatment. Nalbuphine HCL ER is a mixed μ-antagonist and κ-agonist opioid drug was evaluated in hemodialysis patients. Central gating of μ/κ opiate circuitry plays an important role in mediating and countering pruritogenic sensation. However, as a class, kappa opioid agonists have aquaretic effects in both animals and humans, which can be treatment limiting. Nalbuphine HCl ER tablets can be safely administered to HD patients without dose adjustment up to 240 mg BID and may hold promise in treating uremic pruritus.

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