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towards the perilesional area. PKC activity increased in the presence of EOF2 in a novel PKC-dependent manner. In addition, using fusion proteins in which membrane-anchored growth factors neuregulin 1 and TGFα were fused to a eGFP probe at the C-terminal and a to a mCherry probe at the N-terminal, we observed that EOF2 selectively mediated the release of the neurogenic growth factor neuregulin 1 without affecting the release of the gliogenic factor TGFα. Taken together our results dissected the molecular mechanism of a new neurogenic compound with potential clinical issues.

PP.224

Intraocular pressure lowering effect of new formulations of melatonin and agomelatine.

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Glaucoma is a neurodegenerative disease in which an increased intraocular pressure (IOP) is a major risk factor. Lowering IOP is the only proven therapeutic intervention and medical IOP reduction remains the first-line treatment option for the majority of patients. Melatonin (MT) or its analogue agomelatine (AM) have shown significant neuroprotective features and their hypotonizing effect on the IOP have been demonstrated. Here, we evaluated the IOP lowering effect of innovative topical formulations of MT and AM in rats with normal IOP. Different formulations of MT were obtained in PBS, nanolipidic carriers (NLCs) and nanomicelles (NMCs). AM and mixtures of MT and AM were formulated in NMCs. Eye drops were instilled in Wistar rats and their IOP was measured at different time points. All MT eye drops showed a significant IOP lowering effect. The formulation in NMCs gave better and longer lasting effects than the NLC formulation, which in turn was better than the formulation in PBS. AM eye drops also showed an IOP lowering effect, which at the lower concentrations (0.01% and 0.1%) was comparable to that of MT while at 1% appeared more effective than the equivalent MT formulation. Finally, the association of MT and AM demonstrated a long-lasting effect than MT or AM given alone. Interestingly, an anecdotic observation on a single glaucoma patient in which eye drops with MT and AM were added to the standard therapy showed a further 25% IOP reduction after MT and AM thus suggesting that MT and AM could be introduced into the therapeutic armamentarium to treat glaucoma. Overall, the present data confirm the IOP lowering effect of MT and its analogues and evidence that NMC formulations may be the more appropriate for delivering MT to the eye. Funded by Sooft Italia SpA.

PP.225

Contribution of GABAA and GABAB receptors in the modulation of contractile activity in human colon.

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Gamma-Aminobutyric acid (GABA) is a transmitter released by enteric interneurons, regulating gut functions, mainly via GABAA and GABAB receptors. So far, its effective role in the gastrointestinal motility remains poorly understood, especially in human colon, where very few studies have been undertaken. We aimed to investigate the role of GABA in the contractility of the circular muscle of human colon by organ-bath technique. GABA (50 M- 5mM) induced dose-dependent excitatory effects, consisting in an increase in the amplitude of spontaneous contractile activity and, at higher concentrations, also of the basal tone. Such effects were antagonized by bicuculline, GABAA-receptor antagonist, by tetrodotoxin, a neural blocker, and by atropine, a muscarinic receptor antagonist. Muscimol, GABAA-receptor agonist, was able to mimic GABA-effects inducing as well contractile responses. Phaclofen, GABAB-receptor antagonist, per se induced an increase of the mechanical spontaneous activity and potentiated the GABA-induced excitatory effects. Moreover, Baclofen, GABABreceptor agonist, induced inhibitory effects sensitive to tetrodotoxin. In conclusion, these results demonstrated that neural GABAA and GABAB receptor activation is one of the multiple mechanism involved in the modulation of mechanical activity in the human colon circular muscle. Activation of GABAA receptors would lead to the release of acetylcholine from excitatory cholinergic neurons, in turn causing contractile responses. GABAB receptors seems to be tonically active increasing the release of inhibitory transmitters from enteric neurons, in turn counteracting the excitatory contractile activity.

PP.226

The potential role of O-GlcNAcylation in diabetes and depression comorbidity

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Diabetes leads to complications involving brain function, including cognitive decline and depression. It is widely accepted that depression is the consequence of an impaired neurogenesis in the gyrus dentatus of hippocampus, but the molecular mechanisms of this process are still poorly understood. Neurogenesis is the process by which neurons differentiate from neural stem cells, and VRAC channels, responsible for the activation of a chloride conductance (IClswell) after cell swelling during the regulation cellular volume, are essential in cell differentiation. It is well established that diabetes leads to increased O-GlcNAcylation (O-GlcNAc) levels in various tissues. OGlcNAc is a reversible post-translational modification of proteins that occurs via conjugation to the monosaccharide N-acetylglucosamine. In the present study, we investigated the behavior of the IClswell current in neuronal-like SHSY5Y cells by whole-cell patch-clamp in the presence of normal or elevated O-GlcNAc levels. The results show that: SH-SY5Y cells express the IClswell current in isotonic conditions; O-GlcNAc elevation did not lead to cell death but lead to a decline of cell metabolic activity and significantly suppressed the IClswell current. Overall, the evidence obtained indicates that O-GlcNAcylation affects the activity of VRAC channels, thus suggesting that O-GlcNAc elevation may impair hippocampal neurogenesis and contribute to the development of diabetes

PP.227

Development of a polarized 3D organoid pancreatic ductular epithelium that recapitulates the normal ductual architecture and function

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Animal models have traditionally offered an important platform for understanding the physiological and cellular basis for tissue dynamics in a complete physiological environment. However, the differences between mice and humans, together with animal models being expensive, difficult and ethically not sustainable for large-scale studies have fostered the use of in vitro culture systems for dissecting the biochemical and physiological bases of tissue responses. This is particularly important for complex tissues such as pancreatic ducts where epithelial cells comprise the majority of ductal cells and tightly regulate transepithelial acid-base secretion of an apical hydroelectrolyte rich in HCO3- (pancreatic juice) into the duodeno and basolateral acid release into the ECM via a series of membrane transporters: the Na^+/H^+ exchanger, the $Cl^-/HCO3^-$ exchangers, the $Na^+/HCO3^-$ cotransporters, the H^+ATPase and the H^+/K^+-ATPase. However, these cells have been difficult to grow with the correct 3D ductual architecture and function. Using the normal pancreatic ductal epithelial cell line, HPDE, we have determined the necessary 3D growth conditions to have them grow as complex tubular structures lined with epithelial cells and ending in a structure similar to pancreatic acini. Here, we characterized these 3D structures for their expression of pancreatic duct markers and for the above transporters involved in their regulation of pHi/pHe homostasis. Future experiments in these pancreatic ductal epithelium organoids will characterize their bicarbonate secretion and the principal transporters involved in this secretion.

PP.228

Lipid accumulation in hepatocytes impairs endothelial cell function in a manner dependent on the grade of hepatic steatosis

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Intercellular interactions play a central role in many pathophysiological processes including non-alcoholic liver disease (NAFLD), a chronic liver disease often associated with obesity and overnutrition. In response to lipotoxic conditions, the endothelium initiates inflammatory responses representing the first step in atherosclerosis. Cell-cell communication is mediated by a complex network and secreted factors play a major role. This study investigated the cellular mechanisms by which steatotic hepatocytes trigger endothelial cell dysfunction in vitro. To this aim conditioned medium from steatotic hepatocytes (HCM) was used to treat endothelial cells. FaO hepatoma cells exposed to different steatogenic agents alone or combined (3h oleate/palmitate-OP; 72h fructose-Fru; 24h TNF) mimic the progression towards more or less severe steatosis in vitro. After treatments, the HCM were incubated with HECV endothelial cells for 24h. Intracellular TG accumulation, cell viability, apoptosis, H2O2 production, oxidative stress markers, and nitric