Extended Abstract

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Joint Event on Down Syndrome, Autism, Brain Disorders & Therapeutics, October 21-22, 2019, Tokyo, Japan - Depression-like behavior and hypomotility in acutely forced swimming rat improved by prokinetic meranzin hydrate from Chaihu-Shugan-San via ghrelin and neurocircuitry

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Depression and Functional Dyspepsia (FD) are characterized by comorbidity, overlap depressed and nausea etc. and specially one-disease-one-drug-one-target with inefficacy. Parted accumulations of depression pathogenesis mediated by α2-adrenoreceptor or ghrelin etc. are considerable but shared little. Antidepressant (A) or prokinetic (P) agents are many but few A&P. Hippocampus or thalamus-coupled depression or FD is countless but void comorbidity. Ancient Gan-Zhu-Shu-Xie (GZSX who's representative TCM is Chaihu-Shugan-San) clued us to get simultaneous antidepressant from prokinetic Meranzin Hydrate (MH) via shared α2-adrenoreceptor in acutely Forced Swimming (FS) rat from homogeneous comparison. Here we via Chaihu-Shugan-San as tool study causalities from monism (FS, MH and ghrelin) to dualism (gut-brain disorder, A&P and shared regulation) and fuse above via 7.0 T fMRI-BOLD signal, compared with well-known mechanism of positive control. Top 3 foci of BOLD following FS rat with depressed behavior and hypomotility (DB&H) are activities of Hippocampus- Thalamus-Basal ganglia (HTB) circuit. A&P MH almost like CSS stimulated deactivation of 4.02-fold for hippocampus and 1.45-fold for thalamus than fluoxetine. Ghrelin antagonist [D-Lys3]-GHRP-6 synchronously inhibited above A&P and BOLD HTB foci. needless to say, prokinetic mosapride only acted on thalamus and basal ganglia and zip for hippocampus. Among HTB, hippocampus is as protagonist for depression and deputy for FD, thalamus is on the contrary, often basal ganglia is as projection to HT consistent with percentage of HTB each from search of PubMed. This functionally novel connection of HTB following acute stress, treatment and regulation highlights (anti) prokinetic unified theory.

Depression-like behavior and hypomotility in acutely forced swimming rat improved by prokinetic meranzin hydrate from Chaihu-Shugan-San via ghrelin and neurocircuitry. Ancient Gan-zhu-shu-xie (GZSX), whose representative traditional Chinese medicine(TCM) is Chaihu-Shugan-San (CSS), may exert antidepressant effects with prokinetic meranzin hydr-ate (MH) via α2-adrenoreceptors within the acute forced swimming (FS) test in rats.Therefore, the most aim of the study is to research the acute antidepressant and prokinet-ic effects of CSS and MH after acutely FS on rats, and its possible mechanisms

Methods: FS rats were treated with CSS, MH, fluoxetine, ghrelin antagonist [D-Lys3]-GHRP-6, and take a series of behavior tests and gastrointestina motility tests, and via 7.0 T fMRI-BOLD signal, compared with well-known mechanism of positive control. FS performance from dysfunctional GZSX [6, 59–61]) are often divided into DB&H [6, 48–49], exhibiting dual gut-brain disorders in an acute stressor as shown in Fig. 1.A-D. This dichotomy also includes MH→P&A and ghrelin→above regulation with antagonists, revealed in three different counterparts. Thedualism of gut-brain disorder, P&A, and their regulation implicated the HTB circuit supported BOLD activation foci. These results are causalities within and between counterparts 1–3, different from depressive comorbidity with somatic disease whose dichotomy is equivocal [11–13, 32–33] in homogeneous studies. To date, an in vivo localized 1H-MRS study at 4.7 T without BOLD signal only coupled acute FS and rapid antidepressant desipramine. We observed BOLD ac-

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tivated hippocampal responses to traditional Chinese medicine using first-line antidepressant fluoxetine as an impression and a connection from activated foci of the insular lobe, cingulate gyrus, and left amygdala cortex using subacute FS-induced visceral hyperalgesia in ovariectomized rats. As described, it simultaneously induced DB&H (IT of 55.6%↑, NC of 20.8%↓, GE 39.1%↓, and InT 40.3%↓) compared with sham. MH affected IT, NC, GE, and INT (28.6%↓, 53.2%↑, 53.9%↑ and 25.1%↑ vs vehicle). P&A actions by MH were attenuated in acute FS after pretreatment with [D-Lys3] –GHRP (ghrelin antagonist). Inside each counterpart, FS, MH, and ghrelin are bisected as gut-brain disorder and P&A, with shared regulation and interaction within the HTB circuit. Counterparts 1–3 represent FS→ pathophysiology, MH→therapy, and ghrelin→shared mechanisms. The inside/outside counterparts indicate causalities. Here, each HTB circuit comprising comorbid-like profiles is different from the 19 other circuits identified from BOLD activated areas associated with pathogenesis, therapy, and pharmacology for single diseases. To date, nosingle compound except ferulic acid and MH are designed as a simultaneous A&P. Further, ghrelin and α2-AR [49] are reported to commonly mediate A&P using distinct regulatorymechanisms. In mapping activated regions, the roles played by the intricate neurovascular couplings of BOLD signal are invaluable but could also be nonspecific or have poor sensitivity. We address which foci are activated supported antagonist studies, using stress and SSRIs as control [17–29]. FS, MH, and ghrelin antagonist [D-Lys3]-GHRP-6 were used for activation and inactivation. Pre-inhibition of HTB matched the BOLD response map. Thenature and signal amplitude (Ke, cluster size or number of voxels) of fluoxetine and mosapride differed from that of MH within the HTB. Mosapride only activated the thalamus and basal ganglia. BOLD signal intensity for MH was > 4.0 and 1.4 times greater than that for fluoxetine within the hippocampus and thalamus, respectively. Fluoxetine-induced c-fos expression within the thalamus contradicts its effects on behavior [70–71]. [D-Lys3]-GHRP-6 inhibited MH-reduced signal intensity by 84.8% and 23.3% within the hippocampus and thalamus, respectively.

Conclusion: These data show that on acute FS-stimulated DB&H, MH-induced rapid A&P, and ghrelin-related regulation coupled to BOLD signals in brain areas before, providing insight into a unified theory of depression pathogenesis and pharmacotherapy.

Note: This work is partly presented at Joint Event on 19th Global Neuroscience and Neurology Conference and 13th Global Neurologists Meeting on Neurology and Neurosurgery November on 07-08, 2019 held at Frankfurt, Germany