Supplementary Information *– The role of the ghrelin/GHS-R1A signaling in non-alcohol drug addictions (REVIEW) - M. Sustkova-Fiserova et al.*

Table S1. PRECLINICAL STUDIES OVERVIEW

Study design	Drug	Results	Drug of abuse	Reference
Drug effect on the ghrelin blood concentrations	**N**	Four-weeks (5 days a week) cigarettes smoke exposure increased acyl-ghrelin blood levels, while desacyl ghrelin remained unaffected (in rats)	Nicotine/tobacco smoke	Tomoda et al. [1]
	N	Total ghrelin blood levels were not affected by the four-weeks cigarettes smoke exposure (in rats)	Nicotine/tobacco smoke	Ypsilantis et al. [2]
	N	(Total) ghrelin serum levels were increased following 3-weeks of nicotine administration (oral, inhaled, intraperitoneal) (in rats)	Nicotine	Ali et al. [3]
	S	Total ghrelin blood levels were increased following drug single dose administration (in rats)	Methamphetamine	Crowley et al. [4]
	S		Methamphetamine and high doses of MDMA	Kobeissy et al. [5]
	S	Drug IVSA and extinction/anticipation significantly increased both acyl- and desacyl ghrelin blood levels (in rats) Blockade of peripheral adrenergic ß1 receptors by atenolol attenuated the elevation in circulating ghrelin induced by cocaine	Cocaine	You et al. [6, 7]
	S	Total ghrelin blood levels positively correlated with cue-induced cocaine-seeking behavior (in rats)	Cocaine (cue)	Tessari et al. [8]
	C	Intra-gastric drug administration increased total ghrelin blood levels (in rats)	Cannabis extract	Mazidi et al. [9]
	C	Systemic drug administration increased total ghrelin blood levels (in rats)	Synthetic cannabinoids Methanandamide and CP55,940	Zbucki et al. [10]
Acyl-ghrelin administration effects	**N**	Ghrelin amplified the nicotine-induced dopamine release in striatum slices (in vitro rat brain slices)	Nicotine	Palotai et al. [11]
	S	Systemic pretreatment with acute ghrelin augmented/sensitized acute cocaine-induced hyperlocomotion (in rats)	Cocaine	Wellman et al. [12]
	S	Systemic pretreatment with repeated ghrelin augmented/sensitized acute cocaine-induced hyperlocomotion (in rats)	Cocaine	Wellman et al. [13]
	S	Central (NAC-core) pretreatment with ghrelin augmented/sensitized acute drug-induced hyperlocomotion (in rats)	Cocaine	Jang et al. [14]
	S	Central (NAC-core) pretreatment with ghrelin augmented acute drug-induced hyperlocomotion and in co-administration with D1-agonist also the drug-induced behavioral senzitization (in rats)	Amphetamine	Jang et al. [15]
	S	Systemic pretreatment with ghrelin increased development of drug-induced place preference (CPP) (in rats)	Cocaine	Davis et al. [16]
	S	Central (VTA) pretreatment with ghrelin increased development of drug-induced place preference (CPP) (in rats)	Cocaine	Schuette et al. [17]
	S	Central (VTA and NAC) pretreatment with ghrelin increased development of drug-CPP and this was attenuated when JMV2959 was centrally co-administered with ghrelin (in rats)	Cocaine	Dunn et al. [18]

	S	Systemic and central (VTA) ghrelin augments cocaine-enhanced alcohol consumption (in rats)	Cocaine (alcohol)	Cepko et al. [19]
	O	Central (intracerebroventricular) pretreatment with acyl-ghrelin increased drug intravenous self-administration (IVSA) and drug-seeking (in rats)	Heroin	Maric et al. [20]
	C	Systemic acyl-ghrelin increased the drug intravenous self-administration and drug-seeking behavior	Synthetic cannabinoid WIN55,212-2	Charalambous et al. [21]
GHS-R1A antagonist administration	**N**	Systemic JMV2959 pretreatment decreased the drug-induced hyperlocomotion, conditioned place preference expression (CPP) and accumbens dopamine release (in mice)	Nicotine	Jerlhag and Engel [22]
	N	Systemic JMV2959 pretreatment decreased the drug-induced behavioral sensitization	Nicotine	Wellman et al. [23]
	S	Systemic JMV2959 pretreatment decreased the drug-induced hyperlocomotion (in mice)	Cocaine and Amphetamine	Jerlhag et al. [24]
	S	Systemic JMV2959 pretreatment decreases the expression of drug-induced conditioned place preference expression (CPP) and accumbens dopamine release (in mice)	Cocaine and Amphetamine	Jerlhag et al. [24]
	S	Repeated systemic JMV2959 pretreatment decreases the drug-induced hyperlocomotion (in mice)	Amphetamine	Suchankova et al. [25]
	S	Systemic JMV2959 reduced systemic drug-induced increase of dopamine in the NAC-shell and in the VTA (in rats)	Amphetamine	Edvardsson et al. [26]
	S	Systemic repeated JMV2959 together with cocaine decreased the drug-induced behavioral sensitization (in rats)	Cocaine	Clifford et al. [27]
	S	Systemic JMV2959 pretreatment decreased the drug intravenous self-administration (IVSA) and drug-seeking behavior, plus the expression and also development of drug-induced conditioned place preference (CPP) (in rats)	Methampheta mine	Havlickova et al. [28]
	S	Systemic JMV2959 pretreatment decreased the drug-induced CPP, as well as the body weight gain. However, acyl-ghrelin antibodies administration attenuated the weight gain but not the cocaine-CPP, which indicated, that the GHS-R1A effects on reward are independent from peripheral acyl-ghrelin binding. (in mice)	Cocaine	Wenthur et al. [29]
	S	Systemic JMV2959 pretreatment dose-dependently inhibited drug-IVSA, drug-seeking, and reinstatement of drug-seeking triggered by the drug (in rats)	Cocaine	You et al. [6]
	S	Systemic JMV2959 pretreatment inhibited the brain stimulation reward (BSR) and drug-potentiated BSR maintained by optogenetic stimulation of VTA dopamine (in mice)	Cocaine	You et al. [6]
	O	Systemic JMV2959 reduced systemic drug-induced increase of dopamine in the NAC-shell and hyperlocomotion, also it increased accumbens dopamine metabolism by MAO (in rats)	Morphine	Sustkova-Fiserova et al. [30]
	O		Fentanyl	Sustkova-Fiserova et al. [31]
	O	Systemic JMV2959 pretreatment decreased the expression of drug-induced conditioned place preference expression (CPP), hyperlocomotion and accumbens dopamine release (in mice)	Morphine	Engel et al. [32]
	O	Systemic JMV2959 reversed both the acute and sub-	Morphine	Sustkova-

		chronic systemic drug-induced increases in anandamide/AEA levels in the NAC, intensified acute drug-induced decreases in 2-AG levels but attenuated the sub-chronic drug-induced accumbens 2-AG decreases		Fiserova et al. [33]
	O	Acute systemic JMV2959 and also central JMV2959 (VTA and NAC-shell) reversed the drug-induced anandamide/AEA increases in the NAC shell, and intensified drug-induced decreases in the NAC shell 2-AG levels, with both JMV2959 effects more expressed when administered into the NAC shell in comparison to the VTA. JMV2959 pre-treatment also decreased the drug-evoked accumbens GABA efflux (in rats)	Fentanyl	Sustkova-Fiserova et al. [34]
	O	Systemic JMV2959 reduces systemic subchronic drug-induced accumbens dopaminergic sensitization and behavioral sensitization and also drug-induced conditioned place preference (CPP) expression (in rats)	Morphine	Jerabek et al. [35]
	O	Systemic JMV2959 prevented the drug-induced memory reconsolidation and relapse-like behavior in the modified CPP method (in rats)	Morphine	Zhao et al. [36]
	O	Systemic JMV2959 pretreatment decreases the drug intravenous self-administration (IVSA) and drug-seeking behavior, plus the expression and also development of drug-induced conditioned place preference (CPP) (in rats)	Fentanyl	Sustkova-Fiserova et al. [31]
	O	Central (intracerebroventricular) D-Lys3-GHRP6 pretreatment had no effect on drug intravenous selfadministration (IVSA) or food deprivation-induced reinstatement of drug seeking	Heroin	Maric et al. [20]
	O	Central (into VTA) JMV2959 pretreatment decreased the drug-seeking in food restricted rats	Heroin	D´Cunha et al. [37]
	C	Systemic JMV2959 pretreatment decreased the systemic drug-induced hyperlocomotion in rats	THC, synthetic cannabinoid WIN55,212-2	WIN55,212-2 - Charalambous et al. [38] THC - Charalambous et al. [21]
	C	Systemic JMV2959 pretreatment decreased the drug intravenous self-administration (IVSA) and drug-seeking behavior, plus the expression and also development of drug-induced conditioned place preference (CPP) (in rats)	THC for CPP and WIN55,212-2 for IVSA	Charalambous et al. [21]
	C	Systemic JMV2959 pretreatment decreased the central (into VTA) drug-induced dopamine increase, anandamide/AEA and 2-AG increase and reversed the drug-induced GABA decrease in the NAC shell	synthetic cannabinoid WIN55212,2	Charalambous et al. [38]
GHS-R1A knockout animals	**S**	GHS-R1A gene knockouts show reduced drug-induced behavioral sensitization (rats)	Cocaine	Clifford et al. [27]
Ghrelin peptide gene (GHRL) knockout animals	**S**	GHRL gene knockouts showed reduced drug-induced hyperlocomotion as well as reduction of behavioral sensitization dopamine content in striatal dissections (30 min after cocaine) did not differ between GHRL knockouts and wild mice	Cocaine	Abizaid et al. [39]

Table S2. CLINICAL STUDIES OVERVIEW

Study design	Drug	Results	Substance	Reference
Genetic study	**N**	Two haplotypes of the GHSR gene were associated with smoking status (Swedish population)	Nicotine/tobacco	Landgren et al. [40]
	N	Minor allele of the SNP located on the GHSR-1A gene (GHSR) but not on the pre-proghrelin gene (GHRL) appeared to be associated with increased severity of cigarette smoking (Swedish population)	Nicotine/tobacco	Suchankova et al. [41]
	S	No association between pre-proghrelin gene (GHRL) variations and the drug dependence, but correlation between SNP on GHRL and emotional problems (depression, anxiety) was found (Korean population)	Methamphetamine	Yoon et al. [42]
	S	SNP located on the ghrelin receptor gene GHSR seemed associated with the drug dependence; no differences were found between drug-dependent and healthy participants in SNP on the pre-proghrelin gene (GHRL) (Swedish population)	Amphetamine	Suchankova et al. [43]
Ghrelin blood levels	**N**	Chewing nicotine gum in healthy non-smokers did not affect the blood total/desacyl ghrelin levels	Nicotine	Kroemer et al. [44] Pilhatsch et al. [45]
	N	Acute cigarette smoking did not affect total ghrelin levels in non-smokers, but ghrelin was significantly reduced in saliva	Nicotine/tobacco	Kaabi and Khalifa [46]
	N	Acute cigarettes smoking decreased total ghrelin levels in non-smokers (no effect in habitual smokers)	Nicotine/tobacco	Kokkinos et al. [47]
	N	Acute cigarette smoking increased total ghrelin levels in smokers and non-smokers	Nicotine/tobacco	Bouros et al. [48]
	N	Higher fasting total ghrelin serum levels in active smokers than in former and never-smokers (German population)	Nicotine/tobacco	Wittekind et al. [49]
	N	No correlation was found between total ghrelin and tobacco smoking (habituated smokers) (Finish population//Poykko et al)	Nicotine/tobacco	Bouhours-Nouet et al. [50] Kokkinos et al. [47] Poykko et al. [51]
	N	Concentration of acyl-ghrelin, but not total ghrelin, was significantly higher in habituated smokers than in non-smokers	Nicotine/tobacco	Koopmann et al. [52]
	N	Increased total ghrelin blood levels were observed in current smokers in comparison to non-smokers	Nicotine/tobacco	Wittekind et al. [49] Fagerberg et al. [53] Langenberg et al. [54] al´Absi et al. [55]
	N	Total ghrelin blood levels may predict the risk of smoking relapse	Nicotine/tobacco	al´Absi et al. [56] Lemieux and al´Absi [57]
	N	Decreases in acyl-ghrelin levels during abstinence from	Nicotine/tob	Lee et al.

		tobacco in comparison to levels prior to smoking cessation	acco	[58]
	N	In comparison to non-smokers, active smoking seemed to be positively associated with total ghrelin levels, which were attenuated during smoking withdrawal	Nicotine/tobacco	al´Absi et al. [55]
	S	In children with ADHD the total ghrelin blood levels were increased after two months treatment with the drug in comparison to basal pretreatment levels	Methylphenidate	Sahin et al. [59]
	S	No significant effect of intravenous drug administration in experienced cocaine users on the acyl- or total ghrelin blood levels was observed	Cocaine	Bouhlal et al. [60]
	O	No significant differences in plasma acyl- and desacyl ghrelin blood levels between opioid problematic users and healthy controls was found as well as no associations with opioid craving (Turkish population)	Heroin	Kara [61]
	C	Total ghrelin blood levels were increased in chronic drug smoking HIV patients	Chronic THC smokers	Riggs et al. [62]
	C	Total ghrelin blood levels were increased after oral drug administration in healthy cannabis users	Cannabis	Farokhnia et al. [63]
	C	Total ghrelin blood levels were higher after oral drug administration in comparison to smoked and vaporized drug; no significant effects on acyl-ghrelin were found	Cannabis	Farokhnia et al. [64]
	C	Vaporized drug-AUC positively correlated with total ghrelin-AUC and similar trend-positive correlation of drug-AUC with acyl ghrelin AUC was observed	THC	Farokhnia et al. [64]

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