FIGURE 1 Schematic diagram

TABLE 1. Rodent models: unraveling the molecular mechanism for increased alcohol consumption in adolescence following prenatal alcohol consumption

Study	Prenatal study	Adolescent test day/treatment	Measurement/results	Proposed mechanism
Abate, Hernández-Fonseca, Reyes-Guzmán, Barbosa-Luna, and Méndez (2014), Abate et al. (2017)	Wistar rat 2 g/kg GD 17–20	PND 14 10% Intraoral infusion PND 30 Intraoral infusion	Increased intake Increased Met-enk concentration in the PFC, CP, hypothalamus and the hippocampus Decreased Met-enk in VTA	Induced anxiety-like behavior
Chang et al. (2015)	Sprague Dawley 1 g/kg GD 10–15	PND 15, 40 (M only) 20% Intermittent access (14 hr, 6 mins and 30 min)	Increased intake Increased MCH/MCH+, CCR/CCR2+/BrdU+	Behavioral disorders that induces increases alcohol consumption
Chang et al. (2018)	Sprague Dawley 2 g/kg GD 10–15	PND 35 (F), PND 40 (M) 20% Intermittent access (14 hr, 6 min and 30 min)	Increased alcohol intake Increased MCH/MCH+, CCR/CCR2+	Induced anxiety-like behavior
Díaz-Cenzano and Chotro (2010)	Wistar rat 2 g/kg G17-20	PND 14, 26–27 Intraoral infusion 6% (2 BC)	Increased intake Increased preference	Appetitive learning induced by the opioid system

Study	Prenatal study	Adolescent test day/treatment	Measurement/results	Proposed mechanism
Fabio et al. (2015a, 2015b)	Wistar rat 2 g/kg G17-20	PND 35–37 1.25, 2.5, and 3.25 g/kg PND 37–62 4 weeks (3 session/week, 18 hr/session) 5% (2 BC)	Increased ethanol intake Decreased positive c-fos cells in the infralimbic prefrontal cortex Increased intake Increased preference increase dopamine activation in the VTA induced c-FOS activation in AcbSh and AcbC Increase MOR mRNA expression in the VTA	PAE reverses the valence of KOR activation from aversive to appetitive EE was associated with insensitivity to the aversive effects of ethanol, and alterations in MOR mRNA expression in the VTA.
Nizhnikov et al. (2014, 2016)	Sprague Dawley 1 g/kg G17-20	PND 14 PND 42 Intraoral infusion (5, 10, and 20%)	Increased intake Decreased kappa opioid expression in the nucleus accumbens, amygdala and hippocampus	Attenuation of sensitivity of ethanol-induced hyponosis
Eade et al. (2010), Middleton et al. (2009), Youngentob et al. (2007)	Long Evans rats 35% of daily calorie intake G11-20	P30 P42–48 0.313, 0.625, 1.25, 2.5, 5% Vapor saturation	Increased unconditioned response to ethanol odor Decreased GABA receptor, mGluR2 receptor, Caskkin and SOX11 genes	Attenuated aversion by making it taste and smell better

Note: Preclinical studies are ordered alphabetically by the authors.

Abbreviations: AcbC, nucleus accumbens core; AcbSh, nucleus accumbens shell; BC, bottle choice; BrdU, 5-bromo-2-deoxyuridine; CCR/CCL2+, chemokine-C□C motif ligand/receptor; CP, caudate putamen; GABA, gamma-aminobutyric acid; GD, gestational day; KOR, κ-opioid receptor; MCH/MCH+, melanin-concentrating hormone/receptor; Met-enk, met-enkephalin; mGluR2, Group II metabotropic glutamate receptors; MOR, μ-opioid receptor; PFC, prefrontal cortex; PND, postnatal day; SOX11, SRY-related HMG-box gene 11; VTA, ventral tegmental area.

8 CONCLUDING COMMENTS AND FUTURE DIRECTIONS

The endocrine system and neurons in the brain are plastic and can be programmed adversely following prenatal insults during early development. The effect of PAE on the endocrine system results in metabolic dysregulation, while its impact on the brain results in alcohol use disorders. PAE alters the brain's reward system such that a withdrawal from the drug will stimulate the offspring to crave it, which could result in ALD. AA has been found to reinforce these behaviors and attitudes toward ethanol. Given that amniotic fluid and breast milk can program positive appetitive responses in offspring due to the presence of AA, it will be essential to determine if breast milk alcohol is sufficient to program offspring to increased alcohol intake. In this regard, a first step has been taken to ascertain whether breast milk alcohol can program increased alcohol consumption and ALD in later life. It will also be satisfying to understand the immediate effect (before birth) of PAE on opioid system receptors. Adolescence is a critical stage of development when brain growth continues yet it is also a period of vulnerability and stress. Given that an individual's genetic make-up, stress, and anxiety have been found to increase alcohol intake, a predisposition to alcohol in early life will likely exacerbate the propensity to developing ALD. In addition, the current obesity pandemic creates a robust environment which favors the development of the liver disease. Further, alcohol can create a susceptibility to a high-fat diet. Although PAE has often been used as the first hit in ALD, alcohol as a second hit has yet to be explored. Available literature shows that PAE can likely lead to the involuntary onset of alcohol consumption, progress to alcohol dependence and ultimately to ALD.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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