Brain-Derived Neurotrophic Factor val66met genotype interacts with young-adult stress in neurotransmitter regulation of prepulse inhibition in mice

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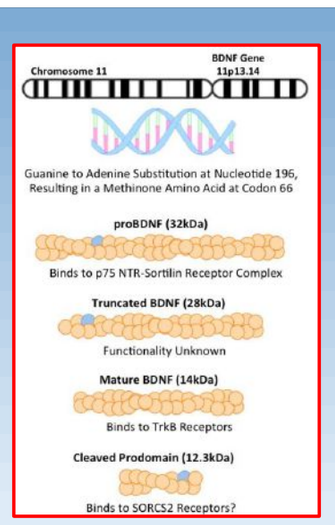
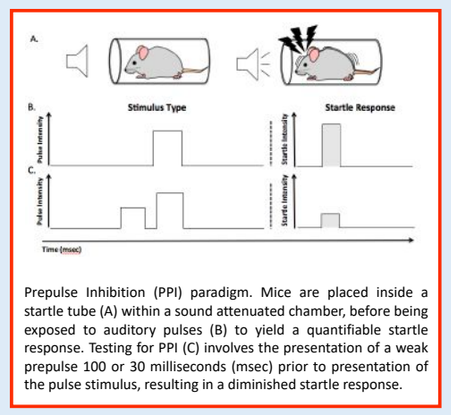
BACKGROUND: Brain-derived neurotrophic factor (BDNF) plays an important role in brain development and neuroplasticity and cognition in adulthood. The common BDNF val66met polymorphism results in reduced activity-dependent BDNF release in the brain and has been implicated in aspects of schizophrenia. BDNF levels in the brain and plasma are altered by developmental stress, which is a well-recognized risk factor in schizophrenia development. However it remains unclear by which neurotransmitter mechanisms the BDNF val66met polymorphism may be involved in schizophrenia.

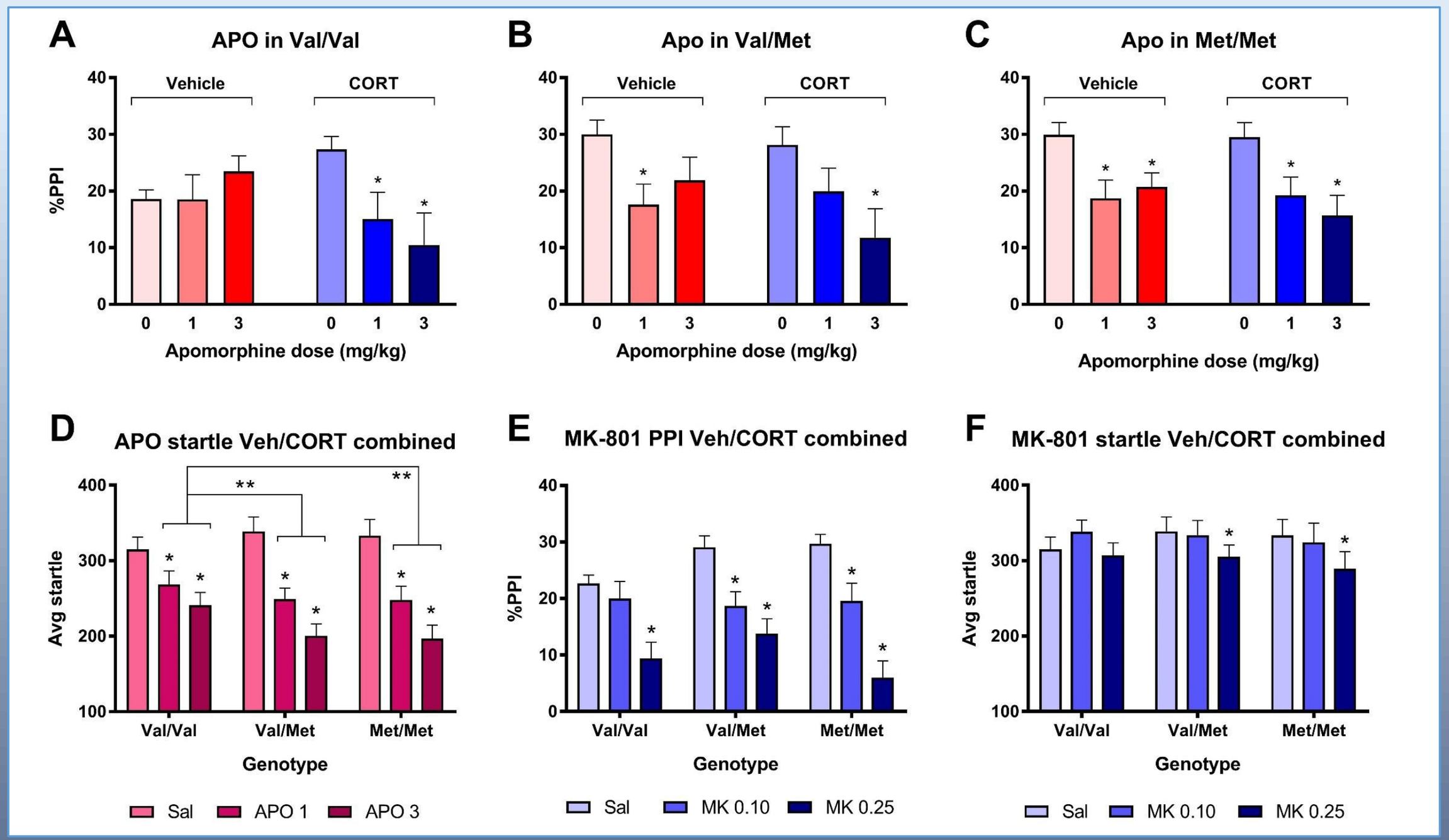


AIM: to investigate the role of the BDNF val66met polymorphism and its interaction with developmental stress in neurotransmitter regulation of prepulse inhibition (PPI), a measure of sensorimotor gating which is disrupted in schizophrenia.

METHODS: We used BDNF^{Val66Met} mice genetically modified to carry a humanized BDNF transcript with the Val66Met polymorphism (hBDNF^{Val66Met}). We studied long-term effect of chronic corticosterone (CORT) exposure (25mg/L drinking water from 6-9 weeks of age) in these animals as a model of history of stress. PPI was assessed in adulthood using standard methodology. We assessed the effects of pseudo-randomized acute treatment with the dopamine receptor agonist, apomorphine (APO), and the NMDA receptor antagonist, MK-801. There were n=18-24 per group with males and females combined; no sex differences were observed in the present study.



Prepulse Inhibition (PPI) paradigm. Mice are placed inside a startle tube (A) within a sound attenuated chamber, before being exposed to auditory pulses (B) to yield a quantifiable startle response. Testing for PPI (C) involves the presentation of a weak prepulse 100 or 30 milliseconds (msec) prior to presentation of the pulse stimulus, resulting in a diminished startle response.



RESULTS: **Apomorphine (APO):** Analysis of the effect of 1mg/kg and 3mg/kg of APO on PPI revealed an APO x CORT interaction and an APO x PP x CORT x genotype interaction, suggesting differential drug effects depending on CORT treatment or genotype. In control Val/Val mice these doses of APO did not affect PPI (A). In contrast, in CORT-pretreated Val/Val mice APO significantly disrupted PPI (A). In Val/Met and Met/Met mice, APO dose-dependently disrupted PPI irrespective of CORT pretreatment (B, C). The effect of APO on startle was greater in Val/Met and Met/Met mice than Val/Val mice independent of prior CORT (D).
MK-801: Acute treatment with MK-801 disrupted PPI (E) and reduced startle (F) independent of genotype or CORT pretreatment.

CONCLUSION: BDNF Val/Met and Met/Met genotypes display greater sensitivity than the Val/Val genotype to disruption of PPI by dopamine receptor stimulation, but not NMDA receptor antagonism. A prior history of stress, here modelled by chronic CORT administration, enhanced the effects of APO in Val/Val mice but had no further effect in the other genotypes which were already responsive to dopamine receptor stimulation-induced PPI disruption. Thus, the BDNF val66met genotype determines sensitivity to dopaminergic disruption of PPI, a model of sensorimotor gating which is an endophenotype of schizophrenia. The BDNF Val66Met genotype also determines differential sensitivity to developmental stress.

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