Analysis of amphetamine-induced BOLD fMRI signals in striatum indicate novel temporal regulation by insulin

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Introduction

Neuropsychiatric disorders such as schizophrenia, attention-deficit/hyperactivity disorder and drug addiction primarily develop through progressive and persistent adaptations in dopamine (DA) transmission in the brain. Once released into the synapse, the effects of DA are limited via high-affinity reuptake mediated by the plasma membrane DA transporter (DAT). Among the various cellular signals that modulate neurotransmitter transport, some of the most novel DAT regulatory pathways are those activated by insulin. DAT-rich brain areas have abundant insulin receptors [1], which sustain DAT expression on the cell surface and increase DA uptake *in vitro* [2]. Moreover, rats depleted of insulin with streptozotocin (STZ) display a reduced ability to clear DA [3] and are markedly insensitive to the expression of behaviors induced by abused compounds such as amphetamine (AMPH) [4], which exert their effects through DAT. Since repeated exposure to psychostimulants is crucial to the development and sensitization of drug dependence, we have now investigated the effect of repeated AMPH treatment on subsequent AMPH-evoked brain activation under normal and hypoinsulinemic conditions.

Methods and Results

Functional magnetic resonance imaging (fMRI) was used to study blood oxygenation level-dependent (BOLD) responses of STZ-treated, hypoinsulinemic animals to acute as well as chronic AMPH adminstration. STZ-pretreated (65 mg/kg/IV, 7 d prior to the start of experiments) rats underwent multislice gradient echo imaging of the forebrain at 9.4T. Two groups of STZ animals were used in these studies: one group had no prior history of AMPH exposure; the other group received four every-other-day systemic injections of AMPH (1.78 mg/kg/IP) and were challenged with AMPH three days after the last injection. Figure 1 shows BOLD activation maps—collected in untreated control (top panels) versus STZ-treated, insulin-depleted (bottom panels) animals—and corresponding region-of-interest (ROI) analysis of the striatum, which reveal differential brain activation in response to acute and chronic AMPH. Compared to saline (*A,D,G*), untreated control rats exhibited robust BOLD signal increases in response to AMPH challenge within the dorsolateral striatum (*B,H*), which were absent in STZ-treated, hypoinsulinemic subjects (*E,H*). In sharp contrast, control rats with a history of repeated, intermittent AMPH exposure exhibited an AMPH-evoked striatal BOLD response (*C,I*) that was completely normalized in STZ-treated rats with the same history of repeated AMPH exposure (*F,I*).

Fig. 1

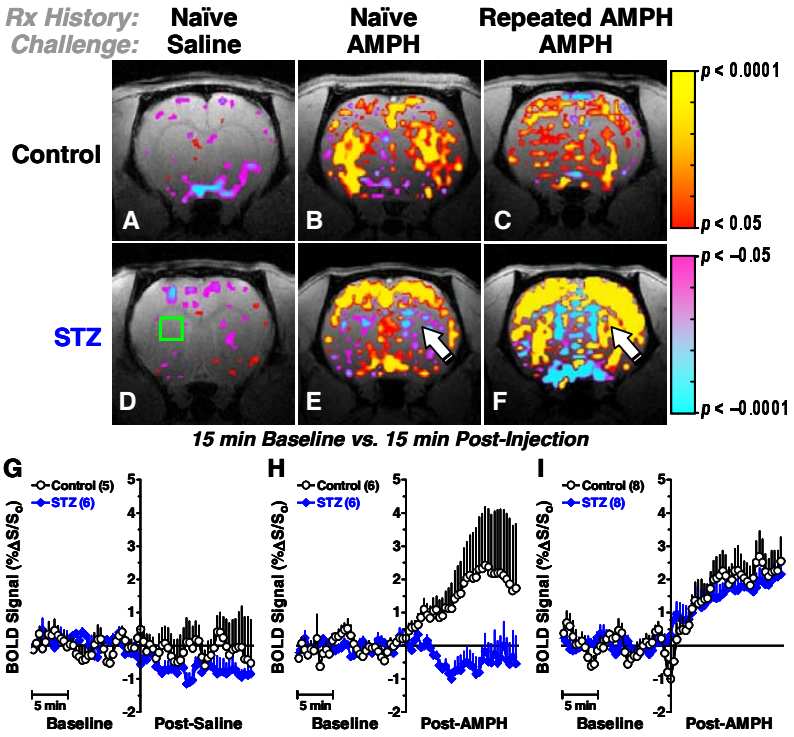

Fig. 1 Representative brain maps depict striatal BOLD responses to saline (*A,D*) or AMPH (*B-C,E-F*) in untreated control (*A-C*) and STZ-treated, hypoinsulinemic (*D-F*) rats. Corresponding group ROI analysis shows striatal BOLD signal fluctuations in saline- (*G*), acute AMPH- (*H*) and repeated AMPH- (*I*) treated control (open circles) and STZ-treated (blue diamonds) rats, n = 5-8. For all subjects square ROIs (e.g. green box in *D*) were drawn over the dorsolateral striatum. Signal intensities from right and left hemispheres (mean ± S.E.M.) were expressed as drift-corrected percentage changes in signal from baseline (%$\Delta S/S_o$).

Conclusions

The current data are among the first *in vivo* evidence that insulin signaling plays an important role in modulating the acute pharmacological actions of psychostimulants. Consistent with previous reports [3], they also imply that insulinergic cascades in brain may themselves undergo temporal adaptations as a result of repeated AMPH administration. Collectively, these and other findings suggest that neuronal pathways engaged by insulin may represent novel targets for the treatment of AMPH-like stimulant abuse and related disorders of DA function. Pharmacological MRI provides a useful tool for quantifying changes in brain DA systems produced by exogenous agents.

References

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