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Prestimulus modification of the startle reflex: relationship to personality and physiological markers of dopamine function

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Abstract

Prepulse inhibition (PPI), a measure of sensorimotor gating, is regulated by dopamine (DA) in rodents. We examined the relationship of PPI in humans to putative markers of brain DA function: (1) novelty seeking (NS; Cloninger's Tridimensional Personality Questionnaire (TPQ)), which is associated with specific DA receptor subtypes, and is reduced in Parkinson's Disease; (2) blink rate, which is increased in primates by DA agonists, and is reduced in Parkinson's Disease. PPI, TPQ and blink rate were measured in 79 normal adult males. A significant negative correlation was observed between resting blink rate and mean PPI, but not between NS and PPI. Blink rate correlated positively with resting EMG level, but this did not account for the relationship between blink rate and PPI. In normal male humans, PPI is inversely related to a physiological marker of resting DA tone (blink rate), but not to a putatively DA-linked personality trait (high NS).

Keywords: Blink; Dopamine; Prepulse inhibition; Sensorimotor gating; Schizophrenia; Startle reflex; TPQ

1. Introduction

Prepulse inhibition (PPI) is the suppression of the startle reflex when a weak prestimulus precedes the startling stimulus by about 100 ms. PPI is an operational

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measure of sensorimotor gating, a process thought to contribute to cognitive integrity in normal humans (Graham, 1975; Blumenthal et al., 1996; Swerdlow, 1996). Evidence that dopamine (DA) regulates PPI in rodents (Swerdlow et al., 1986; Mansbach et al., 1988; Koch and Bubser, 1994; Swerdlow et al., 1994) and humans (Abduljawad et al., 1998; Hutchison and Swift, 1999; Hutchison et al., 1999) is based primarily on PPI changes after pharmacological manipulations. No direct physiological evidence links endogenous brain DA activity to the regulation of PPI.

Endogenous brain DA activity is associated with specific personality and physiological markers. For example, high Novelty Seeking (NS) traits (Cloninger et al., 1991) are associated with specific forms of D2 and D4 DA receptors (Benjamin et al., 2000; Ebstein et al., 1997; Kuhn et al., 1999; Noble et al., 1998; Strobel et al., 1999), and Parkinson's Disease (PD) patients exhibit low NS traits (Jacobs et al., 2001; Menza et al., 1990). There is evidence that eye blink rate (BR) is sensitive to brain DA activity. Specifically: (1) in infra-human primates, BR is increased by DA agonists (Karson et al., 1980; Kleven and Koek, 1996; Lawrence and Redmond, 1991; Taylor et al., 1991), and decreased by DA antagonists (Lawrence et al., 1991; Elsworth et al., 1991) and by striatal DA depletion (Lawrence et al., 1991; Hantraye et al., 1993), with robust correlations ($R = 0.80$) between BR and DA content in the rostral ventromedial caudate nucleus (Taylor et al., 1999). BR is normalized by (1) DA agonists in DA-depleted infra-human primates (Taylor et al., 1991); (2) increased in normal humans by DA agonists (Blin et al., 1990) and in patients with schizophrenia (Stevens, 1978a,b; Karson et al., 1990; Jacobsen et al., 1996; Mackert et al., 1990); (3) reduced in patients with PD but can be increased in these patients with L-DOPA (Hallett, 2000; Karson et al., 1982, 1984). We assessed the relationship between PPI and these putative 'surrogate' markers of endogenous brain DA function: NS traits and BR. If PPI is normally regulated by brain DA activity, individuals with TPQ or BR evidence of high levels of endogenous DA activity should exhibit low levels of PPI.

2. Materials and methods

Eighty three consecutive right handed males (Table 1) enrolled in several different studies of DA agonist effects on startle physiology (IRB #991176). During screening for each of these studies, subjects completed an acoustic startle 'matching test', to assign them to matched active/placebo drug groups, and to exclude 'non-responders' (reflex magnitudes < 50 U (1.22 μV/U); $n = 3$). The present data are from this 'matching test', which was always conducted 7–10 days prior to the drug test. Females were not tested based on normal fluctuations of PPI across the menstrual cycle (Swerdlow et al., 1997). Medical, psychiatric, substance use, social and family histories were obtained by phone screening and by direct interview. Subjects were excluded for a personal history of major mental illness, substance abuse or dependence, recreational drug use in the month prior to the screening, use of any prescription or over-the-counter medications at the time of testing, schizophrenia in a first degree relative, sustained loss of consciousness, severe neurologic or medical