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Novelty-associated locomotion: correlation with cortical and sub-cortical $GABA_A$ receptor binding

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Abstract

The present study was designed to determine whether variability in GABA (η-aminobutyric acid)$_A$ receptor binding in cortical and subcortical brain regions was correlated with locomotor activity in a novel environment. Twenty four animals were rated for locomotor activity in a novel circular runway. Eight days later, locomotor activity was assessed following 1.5 mg/kg amphetamine sulfate (i.p.). After four to six days, animals were killed and samples were pooled in groups of four animals ranked according to novely locomotor score, and specific binding of the $GABA_A$ receptor antagonist [2-(3'-carboxy-2'-propyl)-3-amino-6-*p*-methoxy phenylpyridazinium bromide] ([^{3}H]SR95531) was determined. Significant negative correlations were seen between specific ([^{3}H]SR95531) binding and novelty induced locomotion in the cingulate and prefrontal cortices, and in the ventral pallidum. A near-significant negative correlation was seen in the striatum. Correlation coefficients between locomotion scores in the novel environment and specific [^{3}H]SR95531 binding were: cingulate cortex, $R = -0.91$, $P = 0.012$; prefrontal cortex, $R = -0.85$, $P = 0.032$; ventral pallidum, $R = -0.85$, $P = 0.030$; striatum, $R = -0.73$, $P = 0.097$; and nucleus accumbens, $R = -0.09$, $P = 0.85$. The positive correlation between novelty- and amphetamine-induced locomotion was also quite high ($R = 0.95$, $P = 0.004$). These results are discussed in terms of their relevance to potential biochemmical correlates of drug abuse vulnerability.

Keywords: Individual difference; Novelty; $GABA_A$; Psychostimulant; Cortex; Locomotion; Basal ganglia

1. Introduction

There has been increasing interest in determining biological correlates of behavioral differences between individuals which may relate to vulnerability to drug reinforcement, and the self-administration behavior which it can maintain. Results from several recent studies suggest that novelty-associated locomotion represents an easily measureable behavioral correlate of 'vulnerability' toward drug self-administration in animals, and hence, a potential model for learning more about neurochemical mechanisms of increased vulnerability toward drug abuse. For example, it has been found that novelty-associated locomotion was significantly correlated with both amphetamine-induced locomotion and with the total amount of amphetamine self-administered by rats (Piazza et al., 1989). In addition, locomotion in a novel environment has been associated with a predisposition to develop high ethanol intake (Bisaga and Kostowski, 1993). Other reports indicate that novelty-associated locomotion is significantly related to both amphetamine- and cocaine-induced locomotor activity (Hooks et al., 1991, 1994a; Pap and Bradberry, 1994), and with the ability of psychostimulants to increase extracellular dopamine in the nucleus accumbens (Hooks et al., 1991, 1992a; Bradberry et al., 1991), an action critical to

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their rewarding properties (Roberts and Koob, 1982; Roberts et al., 1977).

Locomotor behavior is regulated by both the mesoaccumbens dopamine system (Fink and Smith, 1980; Kelly and Iversen, 1975; Kelley et al., 1986; Taghzouti et al., 1985) and $GABA_A$ receptors in the ventral pallidum (Mogenson and Nielsen, 1983; Swerdlow and Koob, 1987; Austin and Kalivas, 1990). In addition to a direct modulation of locomotion via actions at the ventral pallidum, it is also possible that actions at $GABA_A$ receptors in cortical areas or the nucleus accumbens could alter locomotion via effects which are in some fashion dependent upon alterations in dopaminergic neurotransmission (Gruen et al., 1992; Austin and Kalivas, 1991; Karreman and Moghaddam, 1996; Klitenick and Kalivas, 1994). It is not clear to what extent the accumbens-pallidal circuitry which mediates the locomotor activating effect of increased accumbens dopaminergic neurotransmission also subserves reinforcement (Robledo and Koob, 1993). Thus, while altered $GABA_A$ receptor binding in the ventral pallidum might not directly impact drug reinforcement, an ability of $GABA_A$ receptor activation in a number of brain regions, including the ventral pallidum to feed back upon accumbens dopaminergic neurotransmission makes this an important receptor site to examine as regards drug reinforcement.

Given the many ways in which $GABA_A$ receptors might influence locomotor behavior, the present study was undertaken to determine if variability in $GABA_A$ receptor binding in cortical and/or subcortical areas, assessed using the $GABA_A$ receptor antagonist [2-(3′-carboxy-2′-propyl)-3-amino-6-*p*-methoxyphenyl pyridazinium bromide] ([^{3}H]SR95531), is associated with individual differences in novelty-associated locomotion. The regions examined were prefrontal cortex, cingulate cortex, the striatum, the nucleus accumbens, and the ventral pallidum.

2. Materials and methods

Twenty four male Sprague-Dawley rats (CAMM; 225–250 g upon delivery) were used as subjects. Animals were housed four per cage, and allowed free access to food and water at all times. Individuals were identified by colored marks on their tails. Two weeks after their arrival as a single group, individuals were tested for locomotion in a novel environment using eight identical chambers, with testing beginning between 09:00 and 10:00 h. Novelty-associated locomotion was assessed using a circular runway (Piazza et al., 1989) which was 10 cm wide, 55 cm outer diameter, with photo beams placed every 90°. Behavior was monitored over a period of 1 h. Total beam breaks were monitored as in the studies of Piazza et al. (1989). Eight days later, the animals were retested in the same apparatus following administration of *d*-amphetamine sulfate (1.5 mg/kg i.p.), which was administered after a 1 h habituation period begun between 09:00 and 10:00 h.

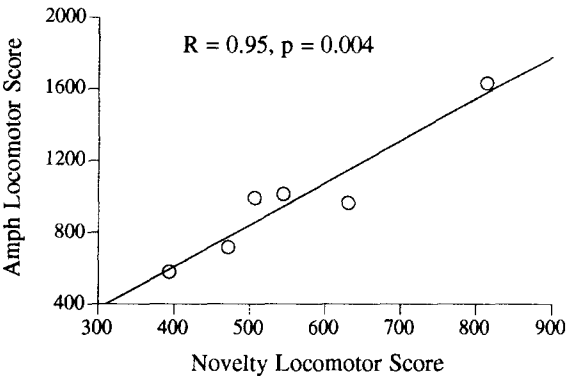
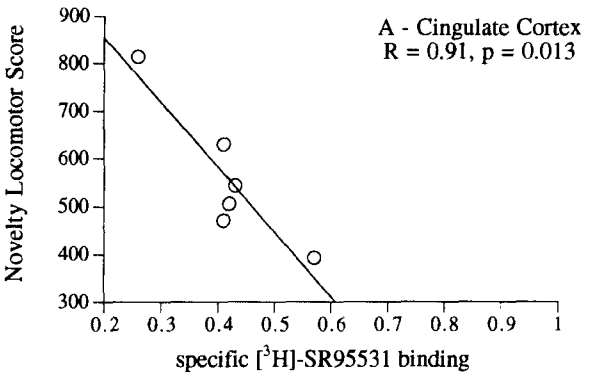


Fig. 1. Correlation between locomotor scores upon first exposure to a circular runway ('Novelty') and those obtained eight days later, with 1-h habituation period prior to amphetamine-SO_4 administration (1.5 mg/kg, i.p., 'Amph'). Beam breaks were totaled over a 1 h period. Twenty four animals were ranked into six groups of four according to novelty locomotor score.

Locomotion following amphetamine was assesed with the same equipment used for determining novelty-associated locomotion. Locomotor scores from each session were



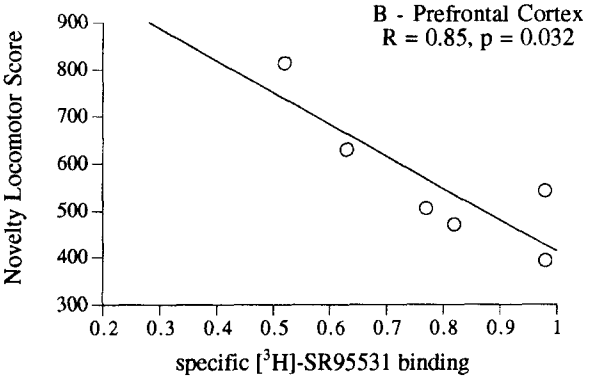


Fig. 2. Correlation between locomotion in a novel environment and specific binding of the $GABA_A$ ligand [^{3}H]SR95531 (pmol bound/mg protein) in (A) cingulate cortex; (B) prefrontal cortex. Twenty four animals were ranked into six groups of four according to novelty locomotor score.

quantified as a single cumulative value based on the number of beam breaks during the 1 h period.

Four to six days after the second test session, animals were sacrificed by decapitation and the following brain areas removed as previously described (Deutch et al., 1985; Gruen et al., 1990): cingulate cortex, prefrontal cortex, striatum, and nucleus accumbens. The ventral pallidum was punch dissected from a 1.0 mm thick coronal section corresponding to anterior: +0.5 mm to −0.5 mm relative to bregma (Paxinos and Watson, 1982), using a 1.6 mm punch. For each brain area, tissue from four animals was pooled to form a single case. This was done to ensure that adequate amounts of tissue were available for assay. Animals were pooled according to increasing rank of novelty-associated locomotion score to form a total of six groups. Killing order followed individual/cage order (evenly spread across ranked groups), not rank order. All samples were frozen at −80°C until assay.

[^{3}H]SR95531 receptor binding was conducted according to the method of McCabe et al. (1988). Samples were homogenized in 10 volumes of 0.32 M sucrose and centrifuged at 3000 rpm for 15 min. The supernatant was resuspended in 10 mM K_2HPO_4/KH_2PO_4 buffer with 100 mM KCl (pH 7.5) and centrifuged at 32 000 × g for 45 min. The P2 pellet was then resuspended in 10 volumes of distilled-deionized water, centrifuged for 30 min at 32 000 × g, resuspended in 10 volumes of 10 mM buffer, and centrifuged at 32 000 × g for 15 min. The final step was repeated and the pellet was resuspended in 10 mM buffer.

Binding was measured in a total volume of 1 ml which consisted of: 100 μl of tissue homogenate, 700 μl of 10 mM buffer, 100 μl of [^{3}H]SR95531 (DuPont NEN; 3 nM), and 100 μl of either 1 mM GABA or buffer. Following a 30 min incubation at 4°C, the tubes were centrifuged at 15 000 rpm for 20 min, and the pellets were rinsed in 1 ml of ice cold 10 mM buffer twice. The pellet was solubilized in 500 μl of Solvable (DuPont, NEN) and dispersed in liquid scintillant.

Specific binding was defined as total binding minus non-specific binding (binding in the presence of 1 mM GABA). As discussed elsewhere (Gruen et al., 1995), a single point binding method was used due to the large amount of tissue needed for assay (approximately 8 mg/tube). Samples from the prefrontal cortex, cingulate cortex, and striatum were assayed in duplicate. Samples from the nucleus accumbens and ventral pallidum were run in singlicate due to the small amount of tissue available (16.5 and 18.2 mg/case, respectively). The reliability of the duplicate values (for the samples from the prefrontal cortex, cingulate cortex, and striatum) was determined using correlational procedures. The average reliability coefficient for the duplicates was 0.95 ($P \leq 0.001$), indicating that the values obtained using this method were highly reliable.

3. Results

Mean novelty- and amphetamine-induced locomotor scores (±S.E.M.) and levels of specific binding in each brain region are presented for the six sub-groups in Table 1. As shown in Fig. 1, the Pearson correlation coefficient between novelty- and amphetamine-induced locomotion was 0.95 ($P < 0.01$).

Fig. 2 (A,B) illustrates the correlations between novelty-associated locomotion and [^{3}H]SR95531 binding in the two cortical regions examined. The correlation coefficients for the cingulate cortex and the prefrontal cortex were −0.91 ($P = 0.0125$) and −0.85 ($P = 0.0315$), indicating that high scores for locomotion in a novel environment were associated with reduced [^{3}H]SR95531 binding. In the subcortical areas examined, the correlation coefficients for the ventral pallidum, striatum and nucleus accumbens were −0.85 ($P = 0.030$), −0.73 ($P = 0.097$) and −0.09 ($P = 0.855$), respectively (see Fig. 3A–C). Examination of the scatterplots representing the correlations between $GABA_A$ receptor binding and novelty-asso-

Table 1
Summary of novelty- (NL) and amphetamine-associated (AL) locomotion scores and specific $GABA_A$ receptor binding from the six groups of animals (four animals per group) ranked by increasing novelty-associated locomotion score

Group	NL (±S.E.M.)	AL (±S.E.M.)	CIN binding	PFC binding	VP binding	STR binding	NAS binding
1	393 (±51)	580 (± 83)	0.57	0.98	0.41	0.4	0.34
2	471 (± 5)	718 (±207)	0.41	0.82	0.3	0.33	0.36
3	506 (± 2)	997 (±243)	0.42	0.77	0.3	0.34	0.22
4	544 (±19)	1017 (±129)	0.43	0.98	0.32	0.27	0.33
5	630 (±12)	970 (±147)	0.41	0.63	0.22	0.26	0.33
6	814 (±40)	1634 (±556)	0.26	0.52	0.22	0.28	0.31

Units of specific binding are pmol [^{3}H]SR95531 bound/mg protein. Abbreviations: CIN, cingulate cortex; PFC, prefrontal cortex; VP, ventral pallidum; STR, striatum; NAS, nucleus accumbens.

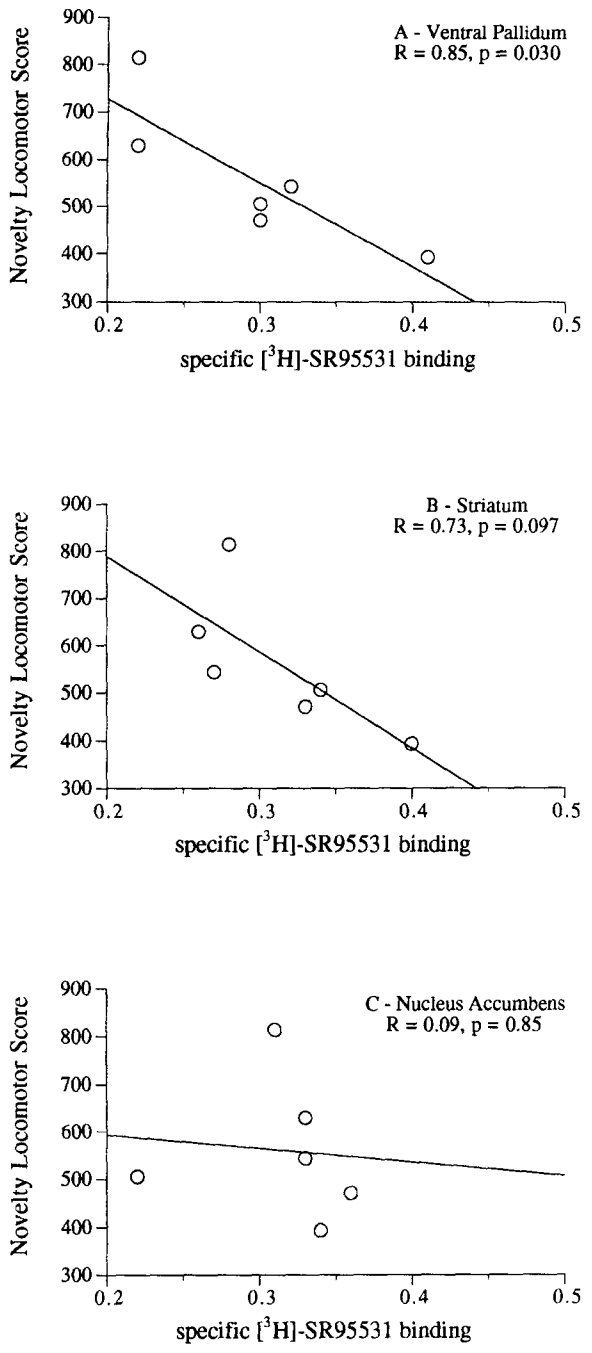


Fig. 3. Correlation between locomotion in a novel environment and specific binding of the $GABA_A$ ligand [^{3}H]SR95331 (pmol bound/mg protein) in (A) ventral pallidum; (B) striatum; (C) nucleus accumbens. Twenty four animals were ranked into six groups of four according to novelty locomotor score.

ciated locomotion indicate that the significant relationships observed were not strongly influenced by outliers.

4. Discussion

This is the first study to demonstrate that a significant correlation exists between novelty-associated locomotion and $GABA_A$ receptor binding. The observed relationships were quite strong; variance in $GABA_A$ receptor binding data from the cingulate cortex, prefrontal cortex, and ventral pallidum was able to account for 82%, 72%, and 73% of the variance in novelty-associated locomotion scores, respectively. A marginally significant relationship was observed in the striatum ($P < 0.10$). There was no correlation seen between novelty-associated locomotion and $GABA_A$ receptor binding in the nucleus accumbens, indicating that the correlations observed were region-specific. Individual differences in specific binding may be due to variations in the K_d, the B_{max}, or both; further research will be needed to clarify this issue. With regard to this question however, an earlier study using mice (Rago et al., 1988) indicated that a significant negative relationship existed between activity in an elevated plus-maze and B_{max} of cortical $GABA_A$ receptor binding. Those results are consistent with the idea that variations between individuals in the $GABA_A$ receptor can play a role in generating overt behavioral differences across a population, with B_{max} a possible source of the differences in $GABA_A$ binding between individuals.

In the present study, novelty-associated locomotion was significantly and positively related to amphetamine-induced locomotion. This is consistent with the results of earlier studies indicating that locomotion in a novel environment is a predictor of both amphetamine- and cocaine-induced locomotion (Hooks et al., 1991, 1992b; Piazza et al., 1989; Pap and Bradberry, 1994). Because novelty-associated locomotion has also been shown to correlate with the vulnerability to acquire amphetamine self-administration (Piazza et al., 1989), the present results with $GABA_A$ binding may have important implications for the neural bases of individual differences in drug reward and self-administration behavior. This is especially so because novelty-associated locomotion correlates with the ability of psychostimulants to increase extracellular dopamine in the nucleus accumbens (Hooks et al., 1991, 1992a; Bradberry et al., 1991) and mesoaccumbens dopaminergic neurotransmission is believed to be critically involved in psychostimulant reward. The intent of this study was to determine which (if any) anatomical regions showed correlations between $GABA_A$ binding and novelty-associated locomotion in order to examine the potential role of $GABA_A$ receptor mediated transmission both within and outside the nucleus accumbens in generating individual differences in novelty and psychostimulant-induced behaviors.

It has been demonstrated that $GABA_A$ receptors in striatum and nucleus accumbens can alter dopamine release (Gruen et al., 1992; Tanganelli et al., 1994; Krebs et al., 1993). However, despite the evidence that $GABA_A$ receptors in the nucleus accumbens can alter dopamine release, the present results would suggest that gradations in $GABA_A$ receptor binding in the nucleus accumbens and striatum do not contribute to differences in novelty-associated locomotion, whereas those in the prefrontal cortex, cingulate cortex, and ventral pallidum might.

Gradations in both cortical and pallidal GABAergic tone are well positioned to alter novelty-, and psychostimulant-induced locomotion. Dopamine neurotransmission in the nucleus accumbens appears to influence locomotion via its ability to inhibit the activity of medium spiny neurons which form a GABAergic inhibitory input to the ventral pallidum where they inhibit ventral pallidum neurons via $GABA_A$ receptors (Mogenson and Nielsen, 1983; Austin and Kalivas, 1990; Swerdlow and Koob, 1987). The potential ability of cortical $GABA_A$ receptors to influence dopaminergic neurotransmission in the nucleus accumbens has been demonstrated in a recent report (Karreman and Moghaddam, 1996) that infusion of the $GABA_A$ receptor antagonist bicuculline into the prefrontal cortex results in increased extracellular dopamine in the nucleus accumbens, apparently through excitatory amino acid feedback mechanisms to the ventral tegmental area. Thus, gradations in cortical, as well as pallidal $GABA_A$ receptor binding could serve as a mechanism mediating enhanced behavioral responses to novelty and psychostimulants. It has previously been demonstrated that animals differing in locomotor response to a novel environment show differences in a number of biochemical markers. (Maccari et al., 1991a,b; Hooks et al., 1994b,c). The question of whether $GABA_A$ receptor binding co-varies with these other markers also shown to be related to novelty-associated locomotion is an obvious avenue for further pursuit, as is the general question of whether there is a key site whose alteration results in changes at the other sites to generate a covarying relationship.

In summary, the present results demonstrate a significant negative correlation between novelty-associated locomotion and $GABA_A$ receptor binding in the prefrontal and cingulate cortices, and in the ventral pallidum. A trend was seen in the striatum, while accumbens binding showed no correlation at all. Both cortical and pallidal reductions in $GABA_A$ receptor actication could potentially increase novelty and psychostimulant-induced locomotion, as well as the reinforcing actions of drugs of abuse via dopaminergic or other mechanisms. These results suggest that the $GABA_A$ receptor should be further investigated as a contributor to individual differences in drug abuse vulnerability.

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