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Dopaminergic Regulation of Anxiety and Stress Coping Responses of Mice Lacking Type 5 Adenylyl Cyclase

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Anxiety is evoked in animals including human beings that are confronted with threatening situations or a novel environment. In normal adaptive states, anxiety allows an animal to remain attentive for the assessment of risk, which is beneficial to the animal' s survival. However, in psychopathological conditions, anxiety can be problematic; animals with pathophysiological anxiety respond to ambiguous or non-harmful stimuli in an exaggerated fashion, since they consider these stimuli to constitute a threatening situation (Martis et al., 2002; Fuchs and Flugge, 2004). The neurological basis and the underlying mechanism of anxiety have yet to be elucidated. One of the most widely accepted neural systems that play a central role in the pathophysiology of anxiety disorders is the g-aminobutyric acid (GABA) system. Benzodiazepines are widely used clinically in controlling anxiety. An increasing body of evidence indicates that neural systems involving dopamine play a role in regulating anxiety-related behavior as well. Animals repeatedly administered with psychostimulants, such as cocaine and amphetamine, display altered behavioral, neurophysiological responses to the drugs (Cancela et al., 2001; Bhattacharya et al., 1997; Millan, 2003). Chronic amphetamine treatment induced an anxiogenic-like response, which can be reversed by haloperidol or SCH23390, suggesting that the dopaminergic system play a role in the control of anxiety (Cancela et al., 2001). Anxiety is also closely interrelated with chronic stress. Repeatedly delivered chronic stress may lead to the development of physical and psychiatric diseases such as anxiety and major depression (McEwen and Steller, 1993; Ader and Cohen, 1993; McEwen, 1998; Wu et al., 2000; Vyas et al., 2002). A recent study reported that dopamine neurons in the midbrain were commonly activated by restraint stress and addictive drugs, suggesting that the midbrain dopamine neurons and their target areas constitute an integrated part of stress responses and addiction (Saal et al., 2003). Collectively, these results suggest that the dopaminergic system may be a candidate neural substrate, which plays an important role in stress coping and anxiety, as well as addiction (Wood, 2004). However, exactly how these interactions and signaling sequences orchestrate the regulation of anxiety and stress response remains unclear. Recently, the molecular genetic approach has made it possible to determine that AC5 is the principal AC, which integrates signals from the D1 and D2 dopamine receptors in the striatum. In the striatum of AC5-/-, over 80% of the forskolin-induced AC activity and 90% of the AC activity stimulated by D1 dopamine receptor agonists are eliminated. However, either the remaining AC activity or non-AC type effector(s) confers various D1 specific pharmaco-behaviors of the AC5-/- mice. In contrast, the signal cascade from D2 to AC was completely abolished in AC5-/-, and the haloperidol-induced suppression of motor activity is absent in AC5-/- (Lee et al., 2002; Iwamoto et al., 2003). Here we provide evidence that AC5-related neural substrates regulate stress coping and anxiety-related behaviors. Mice that lacked the type 5 adenylyl cyclase (AC5) showed tonic anxiolytic-like behaviors in the open field and elevated plus maze tests. The AC5-/- mice displayed remarkably increased locomotion in the open field. The initial locomotor activity of the AC5-/- mice in the open field during the first 20 minutes, which was similar to that of the AC5+/+ mice, was persistent, without habituation, for the first 2 hours of the testing period. The initial locomotor activity of the AC5+/+ mice observed at both the periphery and the center of the open field decayed in a similar time dependent manner. However, the AC5-/- mice spent significantly more time in the center and less time in the periphery compared with their wild type littermates. Furthermore, the exploratory activity of the AC5-/- mice in the center increased over time, which contrasted was sharply with that of the wild type animals. In the EPM test, the control animals showed a preference for the enclosed arm over the open arm in terms of the number of entries and the time spent on each arm, whereas, in the case of the AC5-/- mice examined under the same conditions, no preference for either the open or enclosed arms could be distinguished. It is evident when these data are presented with the percentages of the number of entries and of the time spent in the open and enclosed arms of the EPM. These results suggest that the lack of AC5 produces the anxiolytic-like behavior. The anxiolytic-like response of the AC5-/- mice was reinforced by the D1 receptor agonist DHX, whereas it was extinguished by the D1 receptor antagonist SCH23390. Despite their anxiolytic-like behavioral trait, the AC5-/- mice did not cope the subchronic restraint stress (2 hr/day, 5 days) well; unlike the AC5+/+ mice; the AC5-/- mice showed a dramatic reduction of body weight (82-85% of control) and increased anxiety, and >20% of them were dead under the subchronic restraint stress. The stress-triggered c-Fos induction in AC5-/- was silent in the dorsal striatum, which contrasts sharply with the enhanced c-Fos induction in the corresponding region in the brain of AC5+/+. In the AC5-/- animals that were treated with SCH23390 prior to being subjected to restraint stress, the stress-induced loss of body weight, the c-Fos induction in the striatum and the evoked anxiety reverted to the levels of the untreated AC5-/- mice. These results suggest that the AC5 and D1 dopamine receptor systems constitute a part of the neural substrates controlling both stress coping responses and anxiety-related behaviors.