Supplementary information S1 (box). Animal Models of Resilience

Differential sensitivity to stress has long been noted in laboratory animals: animals showing fewer deleterious effects of stress are considered resilient. Three general approaches have been used: variations observed among a group of outbred or inbred rodents (for example,[1–4]), comparisons across inbred lines of rats and mice (for example,[5]), and selective breeding of rodent lines that display differential stress responses (for example,[6–8]). Animals have also been rendered more or less susceptible to stress by mutation of any of numerous genes[5], corticotropin releasing hormone and its receptors as just one example[9,10]. In each paradigm, susceptible (or vulnerable) animals, which develop certain maladaptive behavioral responses to an acute or chronic stress, are distinguished from unsusceptible (or resilient) animals, which do not exhibit those maladaptive behaviors but in some cases exhibit distinct behavioral adaptations.

Several types of stresses have been used in these studies, and all focus on distinctions between active vs. passive responses to the stress. Researchers have used acute stress paradigms that are widely used to screen compounds for antidepressant-like activity and allow relatively high throughput. For example, in the forced swim and tail suspension tests, an acute dose of an antidepressant increases the time animals spend actively struggling when placed in a beaker of water (rats or mice) or suspended by their tails (mice only). There are large individual or strain differences in the degree to which animals struggle in the absence of antidepressant administration, a fact that has been used to gauge individual sensitivity to stress[5,11]. Of note, immobility in a forced-swim test has also been interpreted as an adaptive strategy to conserve energy, indicating that increased sensitivity to stress established using this paradigm might also be interpreted as increased adaptation. A related paradigm, learned helplessness, where some animals subjected to bouts of inescapable footshock develop deficits in subsequent escape behavior, has also been used to identify active- vs. passive-responding individuals[12–14].

Differential responses to chronic stress have been used as well. Chronic "mild" or unpredictable stress, where rodents are subjected to varying stresses (for example, footshock, restraint, cold stress, etc.) over a period of several weeks, generally induces anhedonia-like symptoms such as reduced sucrose drinking. Inbred C57Bl/6 mice display divergent responses to such chronic stress, with some individuals exhibiting the anhedonia-like symptoms and others not, and with the anhedonia correlating with other behavior deficits such as in the forced swim test[2]. More recently, the chronic social defeat stress paradigm has been applied to this question. C57Bl/6 mice are subjected to social defeat in the home cage of a larger CD1 mouse daily for a period of 10 days. At the end of that defeat stress, a subset of the mice show a stable behavioral syndrome characterized by profound social avoidance, anhedonia, disrupted circadian rhythms, metabolic disturbances, and anxiety-like behavior, which can be alleviated by chronic antidepressant treatment[3,4]. Another subset of mice, subjected to the same degree of defeat, show anxiety-like symptoms but none of the other behavioral abnormalities. These findings emphasize that animals that show resilient-like responses are not oblivious or impervious to the stress, but rather exhibit a distinct, more active set of behavioral adaptations, the underlying neurobiological and molecular mechanisms of which are becoming increasingly well understood[4,15,16].

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