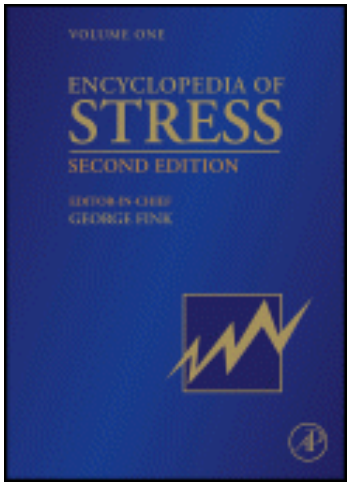

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Crowding Stress

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Glossary

Amyloidosis	A severe pathological change of various organs and tissues during which aggregated amyloid fibers develop and induce the destruction of affected cells.
Channeling	Interaction of enzymes catalyzing consecutive enzyme reactions in which the product of the first reaction becomes the substrate of the second enzyme by a direct molecular transfer largely avoiding free diffusion.
Hypothalamic-pituitary-adrenocortical (HPA) axis	A major mechanism of the stress response, involving three major constituents: the corticotropin-releasing hormone (CRH), corticotropin (ACTH), and glucocorticoids.
Molecular crowding	A term to denote a dense population of molecules (usually macromolecules) where aggregation, diffusion, hydration, and other properties of the individual molecules are significantly altered.
Small and big phenotypes	Small and big phenotypes are well separated in most organisms. Smalls are optimized for low resources (crowded conditions), while bigs are optimized for high resources. These phenotypes are epigenetically inheritable, and their conversion often requires three generations.

Introduction

Studies on crowding stress consider an exceptionally high number of variables. Consequences of crowding stress may differ greatly, depending on whether population density is raised by an increased number of species living in the same area or by reducing their living space. If crowding is increased to such an extent that it leads to confinement, malnutrition, or an increased incidence of infections, other complications develop. Crowding stress may be acute (transient), i.e., the effects manifest after a few days, or chronic, i.e., changes occur after prolonged overcrowding lasting for weeks, months, or even years. Stress conditioning (or stress tolerance) can be observed in crowding stress: repeated stress exposure significantly diminishes the acute stress-induced effects occurring later. While mice or rats are the most commonly used species in crowding stress experiments, studies have been performed with almost all types of domesticated animals, various birds, fishes, and even humans. Though the conclusions of these studies can be directly compared only within the same species, some general trends can be observed. This article focuses on these general aspects of crowding stress.

Crowding Stress: Psychosocial Effects

Crowding as a chronic source of stress constitutes a major threat to psychological well-being. Crowding leads to anxiety and social instability. Dense populations are characterized by considerably increased

aggressive behavior. Crowded monkeys (even well fed), including females and young, have brutal fights, wounding and killing each other. Crowding stress adversely affects gonadal functions, and if it occurs during pregnancy it may inhibit reproductive activity of even the second generation through masculinization of female pups. Chronic crowding leads to deficits in learning tasks and has been used in animal models to induce depression. In human populations, crowding stress evokes prominent psychosocial reactions: it is proposed to be an important factor in the development of increased urban insanity/schizophrenia. Moreover, substance abuse (alcohol, amphetamine, morphine, etc.) and addictive behavior are prompted by a stressful social environment, e.g., crowding stress.

Physiological Changes in Crowding Stress

Recently detailed studies were performed on the effect of crowding on birds. With increased brood size, nestlings of zebra finch *Taeniopygia guttata* grow less, and have decreased testosterone levels and a lower T cell response. These birds are significantly lighter and have shorter wing and tarsus length in adulthood. Females allocate less testosterone in the yolk of their eggs in crowded conditions. This hormone has a positive effect on the growth and muscular development of the embryos. Consequently, newborn birds already start with a growth deficit.

Crowding-related growth deficits can be observed and explained in a wider context. The average height of U.S. men becomes smaller by 1.75 inches (4.5 cm) as the population density increases from 55 persons per square mile to 60 000 persons per square mile. Obviously this change is affected by a large number of variables including the availability of health services, car use/abuse, pollution rates, and stress levels. However, small and big phenotypes seem to be well separated in several species including humans. Smalls are optimized for survival, while bigs were preferentially developed for proliferation. Smalls will develop and succeed under low resources (crowded conditions), while bigs prevail under ample resources (non-crowded conditions). Smalls and bigs properties are coded at the epigenetic level and are not readily interchangeable. As many as three generations may be needed for a phenotype switch from small to big or vice versa. A question for further exciting studies is how acute and prolonged crowding stress affect the switch between these phenotypes.

Crowding stress (especially if chronic) suppresses immune functions. Disturbed immune regulation leads to increased autoantibody levels and may be one of the factors behind the increased occurrence of childhood asthma. Various infections and increased susceptibility to poisoning are more likely to occur under crowded conditions. A widely established example indicates that household overcrowding is related to an increased prevalence of ulcer-inducing *Helicobacter pylori* infections. *H. pylori* infections and stress-induced gastric lesions significantly contribute to the development of ulcers and stomach cancer. Due to digestive problems and occasional appetite loss, chronic stress induces weight loss. In several organs, such as in kidneys and adrenals, chronic crowding stress induces intensive amyloidosis. Chronic overcrowding in many cases leads to hypertension in the resting state or to relative hypertension after exercise.

Possible Molecular Mechanisms of Crowding Stress

Crowding stress activates the hypothalamic-pituitary-adrenocortical axis (HPA axis) and enhances basal level or reactivity of plasma corticosterone secretion. This stress-related stimulation is triggered by the corticotropin-releasing hormone (CRH) system. HPA stimulation by other HPA-related biochemical factors, such as vasopressin, carbachol, and nicotine, is significantly diminished under crowded conditions. Moreover, crowding considerably impairs the HPA axis response to cholinergic and adrenergic stimulations. The mechanism of crowding-induced inhibition is best known in the case of nicotine: social stress affects signal transmission from membrane nicotinic receptors of different subtypes through ion channels into the cell. Crowding stress seems to induce an adaptive response to the non-CRH-induced HPA response to avoid the overstimulation of this important regulatory mechanism.

Repeated, short stresses induced by restraint or crowding attenuate the acute restraint stress-induced stimulatory action of the HPA axis. This indicates the occurrence of stress tolerance (stress conditioning) in the HPA axis response to acute stress. As a possible mechanism a short hypersecretion of corticosterone may induce a prolonged feedback inhibition of the HPA axis activity.

HPA stimulation is possibly the cause of decrease in appetite and consequent weight loss. HPA stimulation leads to compromised immune function and suppression of gonadal functions. The latter effect has an important role in regulation of population size, decreasing the chance of fertilization. Chronic HPA stimulation may lead to osteoporosis, chronic gastrointestinal pain, and retarded growth. Thus, prolonged activation of the HPA axis may explain many of the psychological effects of overcrowding, such as gastrointestinal problems, weight loss, sensitivity to infections, and decreased reproductive activity.

Additionally, crowding stress induces lipid peroxidation and impairs cellular signaling mechanisms, especially in elderly subjects. Impaired signaling may significantly contribute to immune suppression and decreased adaptive mechanisms.

Crowding of Flies and Worms

Signaling mechanisms can be studied more easily in simple organisms. Larval crowding in the fruit fly, *Drosophila melanogaster,* induces HSP (heat shock protein) expression and leads to increased adult longevity and adult thermal stress resistance. Flies that had been exposed to larval crowding exhibit greater starvation resistance and lipid content than populations that did not experience larval crowding. Crowding suffered in larval stage suspends the usual buffering of phenotypic variation: adults of crowded *D. melanogaster* larvae display an increased variability of thorax and wing length, as well as sternopleural and abdominal bristle number.

Food limitation and overcrowding also induce arrested development of the worm, *Caenorhabditis elegans*, leading to the formation of the so-called dauer larva. Daf-7, a homolog of the human transforming growth factor-β (TGF-β), prevents dauer larva commitment. Several other members of the dauer larva regulating Daf family are receptor serine-threonine kinases similar to the human TGF-β receptor. Mutations of another signaling pathway of *C. elegans* may quadruple the adult lifetime of the worm in addition to disturbing its dauer larva development. Thus, disturbances in signaling due to crowding stress may have profound consequences in the longevity of (simpler) organisms.

Cell Crowding

Experimenters often use cell cultures, where the cell density may be much smaller than under physiological conditions. During their proliferation, cells increase their density (in adherent cell lines the culture approaches confluency), and cell crowding may gradually develop. Cell crowding significantly alters the efficiency of autocrine and paracrine hormonal regulation and profoundly changes the influence of neighboring cells as well as the extracellular matrix on the individual cells. Cell crowding usually diminishes cell proliferation. However, tumor cells may escape from this control by expressing various molecules such as integrin αVβ6 or lytic enzymes against components of the extracellular matrix. The extent of cell crowding should be always considered when interpreting the physiological relevance of experimental results with cell cultures.

Molecular Crowding

If the total volume of a macromolecular species occupies a significant fraction of the total volume of the solution, we refer to such a medium as crowded. Under experimental conditions molecular crowding is induced by polyethylene glycol or by dextrane. An intracellular environment, where the total amount of macromolecules usually occupies more than one-third of the total volume, is a typical example of molecular crowding.

Molecular crowding exerts profound quantitative effects on macromolecular interactions in living systems and induces an increased association of macromolecules. Crowding reduces diffusion rates. As a compensatory mechanism, it enhances channeling between enzymes catalyzing consecutive enzyme reactions as well as improves signaling efficiency in organized signaling cascades. By extending the range of intracellular conditions, where macromolecular interactions occur, crowding acts as a metabolic buffer.

Another potential outcome of molecular crowding is the effect on the properties of cellular water. The crowded environment in the cell results in a significant decrease of the proportion of cellular water being in contact with macromolecules such as proteins and DNA. Macromolecules begin to compete for water molecules, their hydration becomes compromised, and, consequently, osmotic stress occurs. The large amount of macromolecules and their immobilized hydrate shell constitute a large excluded volume. Thus, macromolecular crowding affects all those biochemical process in which a change of excluded volume occurs. Such a process is the collapse of newly synthesized polypeptide chain into compact functional proteins, the unfolding of proteins induced by stress, and the association of proteins into nonfunctional aggregates such as plaques in human amyloid diseases.

In conclusion, molecular crowding has a profound effect on the chemistry of life via its influence on association of macromolecules and on the cellular water properties.

Conclusions

Crowding may occur at various levels, from molecules through cells to organisms. Elements of crowded populations have an increased chance for extensive interactions, which increases community formation but may also lead to a high number of unspecific interactions, against which the elements have not previously developed an adaptive response. The unusual effects behave as perturbations of the elements and may lead to their destabilization – thus

crowding stress occurs. Crowding stress profoundly affects the behavior of the element at all levels studied, be it a molecule, a cell, or a simple or higher organism up to humans. Crowding often leads to the reduction of the element number either by diminishing the birth of new elements or by destabilizing, segregating, and/or destroying previously existing elements. This article gave a number of examples of these changes.

See Also the Following Articles

Hypothalamic-Pituitary-Adrenal; Prison; Psychosocial Factors and Stress; Social Stress, Animal Models of.

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Cultural Factors in Stress

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Culture as Adaptation
Cultural Stress
Acculturative Stress

Glossary

Acculturation	A process of cultural and psychological change that results from contact between two cultural groups.
Adaptation	A process of change that seeks to improve the fit between cultural groups and/or individuals and their habitat; it may result in outcomes that range from well-adapted to maladapted.
Culture	A shared way of life of a group of people, including their symbolic, social, and material products; cultures are transmitted to new members over generations.