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Social Relationships and Health

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Recent scientific work has established both a theoretical basis and strong empirical evidence for a causal impact of social relationships on health. Prospective studies, which control for baseline health status, consistently show increased risk of death among persons with a low quantity, and sometimes low quality, of social relationships. Experimental and quasi-experimental studies of humans and animals also suggest that social isolation is a major risk factor for mortality from widely varying causes. The mechanisms through which social relationships affect health and the factors that promote or inhibit the development and maintenance of social relationships remain to be explored.

... my father told me of a careful observer, who certainly had heart-disease and died from it, and who positively stated that his pulse was habitually irregular to an extreme degree; yet to his great disappointment it invariably became regular as soon as my father entered the room.—Charles Darwin (1)

SCIENTISTS HAVE LONG NOTED AN ASSOCIATION BETWEEN social relationships and health. More socially isolated or less socially integrated individuals are less healthy, psychologically and physically, and more likely to die. The first major work of empirical sociology found that less socially integrated people were more likely to commit suicide than the most integrated (2). In subsequent epidemiologic research age-adjusted mortality rates from all causes of death are consistently higher among the unmarried than the married (3–5). Unmarried and more socially isolated people have also manifested higher rates of tuberculosis (6), accidents (7), and psychiatric disorders such as schizophrenia (8, 9). And as the above quote from Darwin suggests, clinicians have also observed potentially health-enhancing qualities of social relationships and contacts.

The causal interpretation and explanation of these associations

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has, however, been less clear. Does a lack of social relationships cause people to become ill or die? Or are unhealthy people less likely to establish and maintain social relationships? Or is there some other factor, such as a misanthropic personality, which predisposes people both to have a lower quantity or quality of social relationships and to become ill or die?

Such questions have been largely unanswerable before the last decade for two reasons. First, there was little theoretical basis for causal explanation. Durkheim (2) proposed a theory of how social relationships affected suicide, but this theory did not generalize to morbidity and mortality from other causes. Second, evidence of the association between social relationships and health, especially in general human populations, was almost entirely retrospective or cross-sectional before the late 1970s. Retrospective studies from death certificates or hospital records ascertained the nature of a person's social relationships after they had become ill or died, and cross-sectional surveys of general populations determined whether people who reported ill health also reported a lower quality or quantity of relationships. Such studies used statistical control of potential confounding variables to rule out third factors that might produce the association between social relationships and health, but could do this only partially. They could not determine whether poor social relationships preceded or followed ill health.

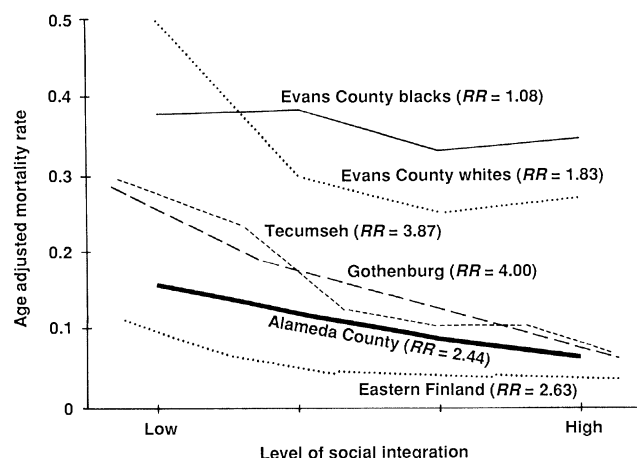


Fig. 1. Level of social integration and age-adjusted mortality for males in five prospective studies. RR, the relative risk ratio of mortality at the lowest versus highest level of social integration.

In this article, we review recent developments that have altered this state of affairs dramatically: (i) emergence of theoretical models for a causal effect of social relationships on health in humans and animals; (ii) cumulation of empirical evidence that social relationships are a consequential predictor of mortality in human populations; and (iii) increasing evidence for the causal impact of social relationships on psychological and physiological functioning in quasi-experimental and experimental studies of humans and animals. These developments suggest that social relationships, or the relative lack thereof, constitute a major risk factor for health—rivaling the effects of well-established health risk factors such as cigarette smoking, blood pressure, blood lipids, obesity, and physical activity. Indeed, the theory and evidence on social relationships and health increasingly approximate that available at the time of the U.S. Surgeon General's 1964 report on smoking and health (10), with similar implications for future research and public policy.

The Emergence of “Social Support” Theory and Research

The study of social relationships and health was revitalized in the middle 1970s by the emergence of a seemingly new field of scientific research on “social support.” This concept was first used in the mental health literature (11, 12), and was linked to physical health in separate seminal articles by physician-epidemiologists Cassel (13) and Cobb (14). These articles grew out of a rapidly developing literature on stress and psychosocial factors in the etiology of health and illness (15). Chronic diseases have increasingly replaced acute infectious diseases as the major causes of disability and death, at least in industrialized countries. Consequently, theories of disease etiology have shifted from ones in which a single factor (usually a microbe) caused a single disease, to ones in which multiple behavioral and environmental as well as biologic and genetic factors combine, often over extended periods, to produce any single disease, with a given factor often playing an etiologic role in multiple diseases.

Cassel (13) and Cobb (14) reviewed more than 30 human and animal studies that found social relationships protective of health. Recognizing that any one study was open to alternative interpretations, they argued that the variety of study designs (ranging from retrospective to experimental), of life stages studied (from birth to death), and of health outcomes involved (including low birth weight, complications of pregnancy, self-reported symptoms, blood pressure, arthritis, tuberculosis, depression, alcoholism, and mortality) suggested a robust, putatively causal, association. Cassel and Cobb indicated that social relationships might promote health in several ways, but emphasized the role of social relationships in moderating or buffering potentially deleterious health effects of psychosocial stress or other health hazards. This idea of “social support,” or something that maintains or sustains the organism by promoting adaptive behavior or neuroendocrine responses in the face of stress or other health hazards, provided a general, albeit simple, theory of how and why social relationships should causally affect health (16).

Publications on “social support” increased almost geometrically from 1976 to 1981. By the late 1970s, however, serious questions emerged about the empirical evidence cited by Cassel and Cobb and the evidence generated in subsequent research. Concerns were expressed about causal priorities between social support and health (since the great majority of studies remained cross-sectional or retrospective and based on self-reported data), about whether social relationships and supports buffered the impact of stress on health or had more direct effects, and about how consequential the effects of

social relationships on health really were (17–19). These concerns have been addressed by a continuing cumulation of two types of empirical data: (i) a new series of prospective mortality studies in human populations and (ii) a broadening base of laboratory and field experimental studies of animals and humans.

Prospective Mortality Studies of Human Populations

Just as concerns began to surface about the nature and strength of the impact of social relationships on health, data from long-term, prospective studies of community populations provided compelling evidence that lack of social relationships constitutes a major risk factor for mortality. Berkman and Syme (20) analyzed a probability sample of 4775 adults in Alameda County, California, who were between 30 and 69 in 1965 when they completed a survey that assessed the presence or extent of four types of social ties—marriage, contacts with extended family and friends, church membership, and other formal and informal group affiliations. Each type of social relationship predicted mortality through the succeeding 9 years. A combined “social network” index remained a significant predictor of mortality (with a relative risk ratio for mortality of about 2.0, indicating that persons low on the index were twice as likely to die as persons high on the index) in multivariate analyses that controlled for self-reports in 1965 of physical health, socioeconomic status, smoking, alcohol consumption, physical activity, obesity, race, life satisfaction, and use of preventive health services. Such adjustment or control for baseline health and other risk factors provides a conservative estimate of the predictive power of social relationships, since some of their impact may be mediated through effects on these risk factors.

The major limitation of the Berkman and Syme study was the lack of other than self-reported data on health at baseline. Thus, House *et al.* (21) sought to replicate and extend the Alameda County results in a study of 2754 adults between 35 and 69 at their initial interview and physical examinations in 1967 through 1969 by the Tecumseh (Michigan) Community Health Study. Composite indices of social relationships and activities (as well as a number of the individual components) were inversely associated with mortality during the succeeding 10- to 12-year follow-up period, with relative risks of 2.0 to 3.0 for men and 1.5 to 2.0 for women, after adjustment for the effects of age and a wide range of biomedically assessed (blood pressure, cholesterol, respiratory function, and electrocardiograms) as well as self-reported risk factors of mortality. Analyzing data on 2059 adults in the Evans County (Georgia) Cardiovascular Epidemiologic Study, Schoenbach *et al.* (22) also found that a social network index similar to that of Berkman and Syme (20) predicted mortality for an 11- to 13-year follow-up period, after adjustment for age and baseline measures of biomedical as well as self-reported risk factors of mortality. The Evans County associations were somewhat weaker than those in Tecumseh and Alameda County, and as in Tecumseh were stronger for males than females.

Studies in Sweden and Finland have described similar results. Tibblin, Welin, and associates (23, 24) studied two cohorts of men born in 1913 and 1923, respectively, and living in 1973 in Gothenberg, Sweden's second largest city. After adjustments for age, baseline levels of systolic blood pressure, serum cholesterol, smoking habits, and perceived health status, mortality in both cohorts through 1982 was inversely related to the number of persons in the household and the men's level of social and outside home activities in 1973. Orth-Gomer *et al.* (25) analyzed the mortality experience through 1981 of a random sample of 17,433 Swedish adults aged 29 to 74 at the time of their 1976 or 1977

baseline interviews. Frequency of contact with family, friends, neighbors, and co-workers in 1976–77 was predictive of mortality through 1981, after adjustment for age, sex, education, employment status, immigrant status, physical exercise, and self-reports of chronic conditions. The effects were stronger among males than among females, and were somewhat nonlinear, with the greatest increase in mortality risk occurring in the most socially isolated third of the sample. In a prospective study of 13,301 adults in predominantly rural eastern Finland, Kaplan *et al.* (26) found a measure of “social connections” similar to those used in Alameda County, Tecumseh, and Evans County to be a significant predictor of male mortality from all causes during 5 years, again after adjustments for other biomedical and self-reported risk factors. Female mortality showed similar, but weaker and statistically nonsignificant, effects.

These studies manifest a consistent pattern of results, as shown in Figs. 1 and 2, which show age-adjusted mortality rates plotted for the five prospective studies from which we could extract parallel data. The report of the sixth study (25) is consistent with these trends. The relative risks (RR) in Figs. 1 and 2 are higher than those reported above because they are only adjusted for age. The levels of mortality in Figs. 1 and 2 vary greatly across studies depending on the follow-up period and composition of the population by age, race, and ethnicity, and geographic locale, but the patterns of prospective association between social integration (that is, the number and frequency of social relationships and contacts) and mortality are remarkably similar, with some variations by race, sex, and geographic locale.

Only the Evans County study reported data for blacks. The predictive association of social integration with mortality among Evans County black males is weaker than among white males in Evans County or elsewhere (Fig. 1), and the relative risk ratio for black females in Evans County, although greater than for Evans County white females, is smaller than the risk ratios for white females in all other studies (Fig. 2). More research on blacks and other minority populations is necessary to determine whether these differences are more generally characteristic of blacks compared to whites.

Modest differences emerge by sex and rural as opposed to urban locale. Results for men and women are strong, linear, and similar in the urban populations of Alameda County (that is, Oakland and environs) and Gothenberg, Sweden (only men were studied in Gothenberg). In the predominantly small-town and rural populations of Tecumseh, Evans County, and eastern Finland, however, two notable deviations from the urban results appear: (i) female risk ratios are consistently weaker than those for men in the same rural populations (Figs. 1 and 2), and (ii) the results for men in more rural populations, although rivaling those in urban populations in terms of risk ratios, assume a distinctly nonlinear, or threshold, form. That is, in Tecumseh, Evans County, and eastern Finland, mortality is clearly elevated among the most socially isolated, but declines only modestly, if at all, between moderate and high levels of social integration.

Explanation of these sex and urban-rural variations awaits research on broader regional or national populations in which the same measures are applied to males and females across the full rural-urban continuum. The current results may have both substantive and methodological explanations. Most of the studies reviewed here, as well as others (27–29), suggest that being married is more beneficial to health, and becoming widowed more detrimental, for men than for women. Women, however, seem to benefit as much or more than men from relationships with friends and relatives, which tend to run along same-sex lines (20, 30). On balance, men may benefit more from social relationships than women, especially in cross-gender relationships. Small communities may also provide a

broader context of social integration and support that benefits most people, except for a relatively small group of socially isolated males.

These results may, however, have methodological rather than substantive explanations. Measures of social relationships or integration used in the existing prospective studies may be less valid or have less variance in rural and small town environments, and for women, thus muting their relationship with mortality. For example, the data for women in Fig. 2 are similar to the data on men if we assume that women have higher quality relationships and hence that their true level of social integration is moderate even at low levels of quantity. The social context of small communities may similarly provide a moderate level of social integration for everyone except quite isolated males. Thus measures of frequency of social contact may be poorer indices of social integration for women and more rural populations than for men and urban dwellers.

Variations in the results in Figs. 1 and 2 should not, however, detract from the remarkable consistency of the overall finding that social relationships do predict mortality for men and women in a wide range of populations, even after adjustment for biomedical risk factors for mortality. Additional prospective studies have shown that social relationships are similarly predictive of all-cause and cardiovascular mortality in studies of people who are elderly (31–33) or have serious illnesses (34, 35).

Experimental and Quasi-Experimental Research

The prospective mortality data are made more compelling by their congruence with growing evidence from experimental and clinical research on animals and humans that variations in exposure to social contacts produce psychological or physiological effects that could, if prolonged, produce serious morbidity and even mortality. Cassel (13) reviewed evidence that the presence of a familiar member of the same species could buffer the impact of experimentally induced stress on ulcers, hypertension, and neurosis in rats, mice, and goats, respectively; and the presence of familiar others has also been shown to reduce anxiety and physiological arousal (specifically secretion of free fatty acids) in humans in potentially stressful laboratory situations (36, 37). Clinical and laboratory data indicate that the presence of or physical contact with another person can modulate human cardiovascular activity and reactivity in general, and in stressful contexts such as intensive care units (38, pp. 122–141). Research also points to the operation of such processes across species. Affectionate petting by humans, or even their mere presence, can reduce the cardiovascular sequelae of stressful situations among dogs, cats, horses, and rabbits (38, pp. 163–180). Nerem *et al.* (39) found that human handling also reduced the arteriosclerotic impact of a high fat diet in rabbits. Recent interest in the potential health benefits of pets for humans, especially the isolated aged, is based on similar notions, although the evidence for such efforts is only suggestive (40).

Bovard (41) has proposed a psychophysiological theory to explain how social relationships and contacts can promote health and protect against disease. He reviews a wide range of human and animal studies suggesting that social relationships and contacts, mediated through the amygdala, activate the anterior hypothalamic zone (stimulating release of human growth hormone) and inhibit the posterior hypothalamic zone (and hence secretion of adrenocorticotrophic hormone, cortisol, catecholamines, and associated sympathetic autonomic activity). These mechanisms are consistent with the impact of social relationships on mortality from a wide range of causes and with studies of the adverse effects of lack of adequate social relationships on the development of human and animal infants (42). This theory is also consistent with sociobiological processes

which, due to the survival benefit of social relationships and collective activity, would promote genetic selection of organisms who find social contact and relatedness rewarding and the lack of such contact and relatedness aversive (43).

The epidemiologic evidence linking social relationships and supports to morbidity in humans is limited and not fully consistent. For example, although laboratory studies show short-term effects of social relationships on cardiovascular functioning that would, over time, produce cardiovascular disease, and prospective studies show impacts of social relationships on mortality from cardiovascular disease, the link between social relationships and the incidence of cardiovascular morbidity has yet to be firmly demonstrated (19, 44). Overall, however, the theory and evidence for the impact of social relationships on health are building steadily (45, 46).

Social Relationships as a Risk Factor for Health: Research and Policy Issues

The theory and data reviewed above meet reasonable criteria for considering social relationships a cause or risk factor of mortality, and probably morbidity, from a wide range of diseases (10; 46; 47, pp. 289–321). These criteria include strength and consistency of statistical associations across a wide range of studies, temporal ordering or prediction from cause to effect, a gradient of response (which may in this case be nonlinear), experimental data on animals and humans consistent with nonexperimental human data, and a plausible theory (41) of biopsychosocial mechanisms explaining the observed associations.

The evidence on social relationships is probably stronger, especially in terms of prospective studies, than the evidence which led to the certification of the Type A behavior pattern as a risk factor for coronary heart disease (48). The evidence regarding social relationships and health increasingly approximates the evidence in the 1964 Surgeon General's report (10) that established cigarette smoking as a cause or risk factor for mortality and morbidity from a range of diseases. The age-adjusted relative risk ratios shown in Figs. 1 and 2 are stronger than the relative risks for all cause mortality reported for cigarette smoking (10). There is, however, less specificity in the associations of social relationships with mortality than has been observed for smoking, which is strongly linked to cancers of the lung and respiratory tract (with age-adjusted risk ratios between 3.0 and 11.0). Better theory and data are needed on the links between social relationships and major specific causes of morbidity and mortality.

Although a lack of social relationships has been established as a risk factor for mortality, and probably morbidity, three areas need further investigation: (i) mechanisms and processes linking social relationships to health, (ii) determinants of levels of "exposure" to social relationships, and (iii) the means to lower the prevalence of relative social isolation in the population or to lessen its deleterious effects on health.

Mechanisms and Processes Linking Social Relationships to Health

Although grounded in the literature on social relationships and health, investigators on social support in the last decade leaped almost immediately to the interpretation that what was consequential for health about social relationships was their supportive quality, especially their capacity to buffer or moderate the deleterious effects of stress or other health hazards (13, 14). Many recent studies have reported either a general positive association between social support

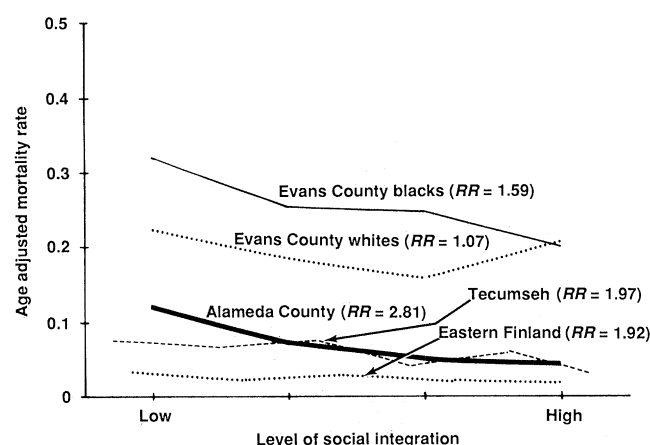


Fig. 2. Level of social integration and age-adjusted mortality for females in five prospective studies. RR, the relative risk ratio of mortality at the lowest versus highest level of social integration.

and health or a buffering effect in the presence of stress (49), but these studies are problematic because the designs are largely cross-sectional or retrospective and the data usually self-reported. The most compelling evidence of the causal significance of social relationships on health has come from the experimental studies of animals and humans and the prospective mortality studies reviewed above—studies in which the measures of social relationships are merely the presence or absence of familiar other organisms, or relative frequency of contact with them, and which often do not distinguish between buffering and main effects. Thus, social relationships appear to have generally beneficial effects on health, not solely or even primarily attributable to their buffering effects, and there may be aspects of social relationships other than their supportive quality that account for these effects.

We now need a broader theory of the biopsychosocial mechanisms and processes linking social relationships to health than can be provided by extant concepts or theories of social support. That broader theory must do several things. First, it must clearly distinguish between (i) the existence or quantity of social relationships, (ii) their formal structure (such as their density or reciprocity), and (iii) the actual content of these relationships such as social support. Only by testing the effects on health of these different aspects of social relationships in the same study can we understand what it is about social relationships that is consequential for health.

Second, we need better understanding of the social, psychological, and biological processes that link the existence, quantity, structure, or content of social relationships to health. Social support—whether in the form of practical help, emotional sustenance, or provision of information—is only one of the social processes involved here. Not only may social relationships affect health because they are or are not supportive, they may also regulate or control human thought, feeling and behavior in ways that promote health, as in Durkheim's (2) theory relating social integration to suicide. Current views based on this perspective suggest that social relationships affect health either by fostering a sense of meaning or coherence that promotes health (50) or by facilitating health-promoting behaviors such as proper sleep, diet, or exercise, appropriate use of alcohol, cigarettes, and drugs, adherence to medical regimens, or seeking appropriate medical care (51). The negative or conflictive aspects of social relationships need also to be considered, since they may be detrimental to the maintenance of health and of social relationships (52).

We must further understand the psychological and biological processes or mechanisms linking social relationships to health, either

as extensions of the social processes just discussed [for example, processes of cognitive appraisal and coping (53)] or as independent mechanisms. In the latter regard, psychological and sociobiological theories suggest that the mere presence of, or sense of relatedness with, another organism may have relatively direct motivational, emotional, or neuroendocrinal effects that promote health either directly or in the face of stress or other health hazards but that operate independently of cognitive appraisal or behavioral coping and adaptation (38, pp. 87–180; 42, 43, 54).

Determinants of Social Relationships: Scientific and Policy Issues

Although social relationships have been extensively studied during the past decade as independent, intervening, and moderating variables affecting stress or health or the relations between them, almost no attention has been paid to social relationships as dependent variables. The determinants of social relationships, as well as their consequences, are crucial to the theoretical and causal status of social relationships in relation to health. If exogenous biological, psychological, or social variables determine both health and the nature of social relationships, then the observed association of social relationships to health may be totally or partially spurious. More practically, Cassel (13), Cobb (14), and others became interested in social support as a means of improving health. This, in turn, requires understanding of the broader social, as well as psychological or biological, structures and processes that determine the quantity and quality of social relationships and support in society.

It is clear that biology and personality must and do affect both people's health and the quantity and quality of their social relationships. Research has established that such factors do not, however, explain away the experimental, cross-sectional, and prospective evidence linking social relationships to health (55). In none of the prospective studies have controls for biological or health variables been able to explain away the predictive association between social relationships and mortality. Efforts to explain away the association of social relationships and supports with health by controls for personality variables have similarly failed (56, 57). Social relationships have a predictive, arguably causal, association with health in their own right.

The extent and quality of social relationships experienced by individuals is also a function of broader social forces. Whether people are employed, married, attend church, belong to organizations, or have frequent contact with friends and relatives, and the nature and quality of those relationships, are all determined in part by their positions in a larger social structure that is stratified by age, race, sex, and socioeconomic status and is organized in terms of residential communities, work organizations, and larger political and economic structures. Older people, blacks, and the poor are generally less socially integrated (58), and differences in social relationships by sex and place of residence have been discussed in relation to Figs. 1 and 2. Changing patterns of fertility, mortality, and migration in society affect opportunities for work, marriage, living and working in different settings, and having relationships with friends and relatives, and can even affect the nature and quality of these relations (59). These demographic patterns are themselves subject to influence by both planned and unplanned economic and political change, which can also affect individuals' social relationships more directly—witness the massive increase in divorce during the last few decades in response to the women's movement, growth in women's labor force participation, and changing divorce law (60, 61).

In contrast with the 1950s, adults in the United States in the

1970s were less likely to be married, more likely to be living alone, less likely to belong to voluntary organizations, and less likely to visit informally with others (62). Changes in marital and childbearing patterns and in the age structure of our society will produce in the 21st century a steady increase of the number of older people who lack spouses or children—the people to whom older people most often turn for relatedness and support (59). Thus, just as we discover the importance of social relationships for health, and see an increasing need for them, their prevalence and availability may be declining. Changes in other risk factors (for example, the decline of smoking) and improvements in medical technology are still producing overall improvements on health and longevity, but the improvements might be even greater if the quantity and quality of social relationships were also improving.

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The Coupling of Neurotransmitter Receptors to Ion Channels in the Brain

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Recent studies on the action of neurotransmitters on hippocampal pyramidal cells indicate that different neurotransmitter receptors that use either the same or different coupling mechanisms converge onto the same ion channel. Conversely, virtually all of the neurotransmitters act on at least two distinct receptor subtypes coupled to different ion channels on the same cell. The existence of both convergence and divergence in the action of neurotransmitters results in a remarkable diversity in neuronal signaling.

IN THE 1950s THE USE OF INTRACELLULAR RECORDING ESTABLISHED the chemical nature of synaptic transmission in the mammalian central nervous system (1). Specifically, neurotransmitters produce their excitatory and inhibitory effects on neurons by rapidly and briefly increasing membrane ion permeability. Over the past 25 years, the use of iontophoretic techniques, in which drugs can be directly applied onto single neurons in vivo, allowed such compounds as γ -aminobutyric acid (GABA), glycine, glutamate, norepinephrine, acetylcholine (ACh), and serotonin to be identified as neurotransmitters in the mammalian brain (2). However, investigators had to turn to simpler invertebrate preparations for more detailed studies of the mechanisms involved in the action of neurotransmitters. These preparations, as well as preparations of peripheral ganglia from vertebrates, avoided the numerous constraints of in vivo mammalian preparations, such as the complexity of the neuronal circuitry, barriers to drug delivery, and lack of stability for intracellular recording. Investigators were thus able to demonstrate an extraordinary diversity in neurotransmitter action (3). The results to be discussed in this review will demonstrate that studies that could originally only be done in these invertebrate in vitro preparations can now be performed in in vitro slice preparations of the mammalian brain. The slice preparation has the advantage that fully differentiated adult brain tissue, in which the local neuronal circuitry is often intact and functioning, is used.

Although biochemical studies on brain slices have been carried out for over half a century, electrical recordings were first made in

the mid-1960s by Yamamoto (4). The development of the transverse hippocampal slice in which all of the local circuits can be functionally preserved (5), coupled with the demonstration that high quality intracellular recording could routinely be obtained from these slices (6), led to a rapid explosion in the use of brain slice preparations for electrophysiological analysis (7).

Previous results by neurochemists suggested a functional role for a variety of putative neurotransmitters. For instance, in the hippocampus, neurochemical and immunohistochemical studies have found close to 20 different putative neurotransmitters in nerve cell bodies or fibers or both. Specific receptor binding sites for many of these same compounds have been identified and characterized (8). In addition, the brain has long provided the richest source of tissue for biochemists studying various components of second messenger systems (9), which mediate the effects of many neurotransmitters.

I have focused my attention on the hippocampal slice preparation for a number of reasons. There are many neurotransmitter candidates in this cortical structure (Table 1). In addition, the precise laminar organization of cellular components permits much of the local circuitry to remain intact and greatly facilitates intracellular recording and selective stimulation of afferent neuronal pathways. Finally, the hippocampus is of considerable interest in its own right, because it plays a key role in memory (10) and epilepsy (11).

Neurotransmitters exert their effects by opening or closing ion channels in the neuronal membrane, either directly or through the activation of intermediate proteins. Until recently, it was believed that most neurotransmitters produced a simple hyperpolarization or depolarization of brief duration in the postsynaptic membrane. However, it is now known that neurotransmitters can alter, over a longer time span, the properties of voltage-dependent ionic conductances that are involved in the control of cell excitability (3). In particular, a wide range of K^+ currents and Ca^{2+} currents are modulated by neurotransmitters, resulting in such changes as increased action potential duration, changes in firing frequency and firing pattern, and increased Ca^{2+} entry during an action potential. Thus, the modulation of voltage-dependent ion channels allows for a finer control via multiple mechanisms of various aspects of cell excitability.

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