Pharmacologic Activation of Limbic Structures and Neuroimaging Studies of Emotions

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Two primary paradigms have been employed to study the neurobiological basis of human emotions. These are induced emotions in normal subjects and the comparison of patients suffering from emotional disorders with normal control subjects. These traditional methods, which have limitations, may be complemented by a third approach: the experimental elicitation of affect through pharmacologic limbic stimulation with intravenous procaine hydrochloride. In this paper, the authors review their research using the direct stimulation approach. To determine whether procaine produces affectively laden experiences accompanied by a reliable change in brain activity, 10 normal subjects received two injections each of placebo (A) and procaine (B)—in ABBA order—while in a positron emission tomography (PET) scanner. In a further study, emotional responses were observed among 24 subjects (including the 10 subjects in the PET study) for a total of 80 procaine injections. Procaine was shown to induce bilateral activation of an anterior limbic network concomitant with powerful, transient emotional and other subjective phenomena as well as autonomic and endocrine responses. Considerable between-subject variability in responses was noted, suggesting that this method can be used to explore individual differences in the neurobiological basis of emotion and affective disposition. Experimental elicitation of affect through limbic stimulation with procaine, when used as part of a triangulation strategy with traditional imaging paradigms, can contribute to our understanding of emotion and its disorders, of the different components of emotion-response systems (e.g., subjective, autonomic, and endocrine), and of individual differences in affective disposition.

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Understanding the neural substrates of emotions is critical to elucidating the biological underpinnings of emotional disorders and of individual differences in emotional disposition. Recent advances in functional neuroimaging techniques promise to make a critical contribution to this area of research. Two neuroimaging approaches have been successfully used to elucidate the relationship between emotion and neurobiology, i.e., studies of induced emotions in normal subjects and studies comparing brain physiology in patients suffering from emotional disorders with that of normal controls.[1–4] Both methods have confirmed that phylogenetically older brain structures, often referred to as limbic and paralimbic, are implicated in the production and experience of emotional states. These traditional methods, however, have five primary limitations:

1. Emotions induced in the laboratory are typically limited in intensity and in the array and range of physiologic responses that are evoked, making it difficult to generalize from the laboratory setting to naturally occurring emotions.
2. The limited intensity of evoked affects, combined with the limited spatial and temporal resolution of neuroimaging techniques, greatly limits the potential of such studies to probe for differences in regional metabolism or blood flow related to individual differences in affective disposition.
3. It is often difficult to disentangle which aspect of the evoked pattern of brain activation is related to the affective experience and which to the cognitive processing of the emotion-inducing stimuli.
4. The induction procedure—whether using movies, autobiographic memories, or Velten's sugges-

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tion—can be interpreted and experienced quite differently by different subjects.

5. Normal emotional experiences may not implicate the same neural circuits as those underlying the abnormal affective states seen in psychiatric patients.

We believe that these limitations can be addressed by a triangulation strategy using a third approach to studying the neural substrates of emotional states, i.e., the direct pharmacologic stimulation of limbic and paralimbic structures. Prior reports have indicated that intravenous injection of procaine hydrochloride can evoke emotional and somatovisceral experiences as well as cognitive and perceptual effects in normal subjects.[5,6] These experiences are intense and short-lived, and their provocation does not require any particular environmental manipulation or induction of mood.[7] At the biological level, procaine has been shown to induce electrical activity in limbic structures, such as the amygdala,[8] while reducing activity in the neocortex.[9]

A PROCAINE-PET STUDY

To demonstrate that procaine produces affectively laden experiences and that these experiences are accompanied by reliable changes in brain activity, we gave 10 normal subjects two injections each of placebo (A) and procaine (B)—in ABBA order—while the subjects were in the positron emission tomography (PET) scanner.[10] Five minutes after each injection, the subjects were extensively interviewed to obtain information about affective, cognitive, somatovisceral, and perceptual experiences.

Procaine was shown to produce reliable increases in brain activity in bilateral amygdalo/parahippocampal gyri and insular cortices as well as in the full extent of the anterior cingulate cortex. No significant increases in blood flow were noted in the neocortical regions.

Concomitant with this pattern of brain activation, procaine evoked brief but intense affective experiences and, to a lesser extent, cognitive, perceptual, and somatovisceral experiences. The subjects reported a range of affective experiences, including euphoria, sadness, fear, and anxiety as well as perceptual experiences, such as auditory acuity followed by unformed auditory hallucinations (e.g., ringing in the ears). Moreover, procaine produced autonomic and endocrine responses, including a brief increase in heart rate and a significant increase in plasma cortisol.

FURTHER OBSERVATIONS OF PROCAINE EFFECTS

We observed important intersubject as well as intrasubject differences in 24 normal subjects (including those in the PET study described above) during a total of 80 procaine injections.[10] Most of the subjects' emotional responses were consistent across consecutive injections, and yet different subjects had radically different experiences. Some subjects, for example, experienced euphoria while others consistently experienced severe anxiety.

In addition to the differences between subjects, we were struck by the presence of significant intrasubject variability. For example, most subjects who experienced dysphoria reported much more anxiety and discomfort during the first injection in the PET scanner than during prior or subsequent injections.

CLINICAL IMPLICATIONS

Procaine-induced changes in regional cerebral blood flow (rCBF) suggest that the qualia of emotions may originate from activation in an integrated subcortical circuit centered on anterior limbic structures. An important question raised by these findings is whether different patterns of activity in such a limbic network can be identified for different emotions. The fact that procaine evokes different emotions both in different subjects and in the same subjects across different injections provides powerful leverage to explore this question. With sufficient numbers of subjects and with the ever improving spatial resolution of neuroimaging techniques, it should be possible to identify CNS patterns of coactivation that are characteristic of a particular qualia.

Furthermore, procaine challenges may shed light on the subcomponents of emotional states. It is well known that the subjective, autonomic, and endocrine components of emotions are only loosely correlated.[11] Because procaine induces strong responses involving all of these components, it should be possible to identify which subpatterns of CNS activation are associated with each of the different components.

Moreover, the use of pharmacologically induced affect in the absence of valence-directing external stimuli may provide a kind of Rorschach inkblot test for further exploring the basis of individual differences in affective processing. Because procaine-induced responses are subjectively intense and produce strong changes in rCBF that are detectable in individual subjects, it may be possible to interpret the patterns of activation of a given individual as a predictor of affective responses or to follow the course of a particular treatment.

SUMMARY

Intravenous injections of procaine hydrochloride produced intense experiential phenomena in the affective, cognitive, somatovisceral, and perceptual domains as well as in endocrine and autonomic responses. These phenomena were associated with very selective brain activations

in limbic and paralimbic structures that have long been implicated in the experience, expression, and modulation of affect.

We believe that the limitations of the two traditional methods for elucidating the relationship between emotion and neurobiology can be addressed by a triangulation strategy that uses a third approach, i.e., the direct stimulation of limbic and paralimbic structures with intravenous pharmacologic agents, to study the neural substrates of emotional states.

Drug name: procaine (Novocain).

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